The New England
Journal of Medicine

Copyright, 1954, by the Massachusetts Medical Society

Volume 250 JUNE 24, 1954 Number 25

AMEBIC GRANULOMA*

Report of Four Cases and Review of the Literature

CHARLES G. SPICKNALL, M.D.,† AND E. CONVERSE PEIRCE, II, M.D.‡

BALTIMORE, MARYLAND, AND KNOXVILLE, TENNESSEE

REPORTS of cases of amebic granuloma are rare in the North American literature, and no complete review has been published in journals of the United States. At this hospital, in the last five years, we have seen 4 cases among 214 patients with amebic colitis. It is probable that the lesion is not a rare complication of amebiasis, and since the incidence of amebiasis in the United States has been found to be 1.7 to 25.9 per cent,[1] according to the area surveyed, there must be many cases that are not recognized. When these patients are adequately treated with antiamebic drugs the morbidity and mortality rates are low; however, when proper treatment is not given or operation is performed because of a wrong diagnosis, as is frequently done, the disease may be fatal. We consider it important, therefore, to report the following cases and to review the literature as completely as possible with the hope that more cases will be recognized and properly treated.

CASE REPORTS

CASE 1. A.S., a 33-year-old seaman, a native of India, was admitted to the hospital complaining of right-lower-quadrant pain of about 6 hours' duration. He had no history of diarrhea or constipation but had vomited with the onset of the pain.

Physical examination revealed tenderness, rigidity and rebound tenderness in the right lower quadrant, where a firm mass was palpable. Physical examination otherwise was within normal limits.

The temperature was 100°F., and the pulse 105.

The white-cell count was 17,000, with 80 per cent neutrophils and 20 per cent lymphocytes.

A diagnosis of acute appendicitis was made, and an exploratory operation was performed soon after admission. A greatly enlarged, firm cecum with a thickened and friable wall was encountered. Several lymph nodes adjacent to the cecum had a similar appearance. Biopsy of a small section of the cecal wall showed only inflammatory reaction. No amebas were seen. A clinical diagnosis of amebic granuloma of the cecum was made at operation, and the patient was given emetine.

The complement fixation for amebiasis was positive and remained so during the 3 months' hospital stay. Many stool examinations were negative for *Endamoeba histolytica*, but emetine had been given before these were begun. On barium-enema study the tip of the cecum could not be filled. A roentgenogram of the chest was normal, and tuberculin skin tests were negative.

Four weeks after operation the patient had improved somewhat, but the mass and pain in the right lower quadrant persisted. He was given more emetine, followed by Diodoquin (diiodohydroxyquinoline) and carbarsone. Two months after operation because of recurrent vomiting and the persistence of the abdominal mass and pain an exploratory operation was again carried out; the cecum was still enlarged and thickened and could not be removed because it was densely adherent to the posterior wall. An ileotransverse colostomy was done, and the cecum was again biopsied and a lymph node removed. The tissue showed only a nonspecific inflammatory reaction.

After operation the patient gained weight and strength, and the mass became progressively smaller until at the time of discharge it was barely palpable.

This patient presented a typical picture of amebic involvement of the cecum masquerading as acute appendicitis such as is described by practitioners in tropical countries. Prompt recognition of the disease and treatment with emetine probably prevented serious or fatal complications.

There is no histologic proof that the granuloma was amebic in origin. However, the biopsies and reduction in the size of the tumor certainly excluded a neoplasm, and there was nothing to suggest tuberculosis. Although no amebas were seen in the biopsy specimens these were taken from the external surface of the granuloma, where amebas are generally not found. Furthermore, the complement fixation for amebiasis was repeatedly positive.

CASE 2. T.W., a 66-year-old seaman, complaining of the sudden onset of painful diarrhea 8 days previously, was admitted with a diagnosis of carcinoma of the rectum. Before the onset of the present illness the patient had had a formed bowel movement twice a day. He had lived in Maryland all his life.

Physical examination gave evidence of recent weight loss. Abdominal examination was negative. The anal-sphincter tone was poor, and the patient was incontinent of semiliquid feces during the rectal examination, which was very painful. At the tip of the examining finger an irregular, firm, annular lesion was felt. This was hard, fixed and extremely tender. Its lumen did not admit the tip of the

*From the Medical and Surgical services, United States Public Health Service Hospital.

†Instructor in medicine, Johns Hopkins University School of Medicine; chief, Medical Service, United States Public Health Service Hospital.

‡Chief, Surgical Section, Acuff Clinic; formerly, instructor in surgery, Georgetown University School of Medicine, and member, Surgical Service, United States Public Health Service Hospital.

examining finger completely. On proctoscopic examination the mass was visualized at 7 cm. Its surface was of an unusual, dirty-gray color and appeared to be markedly necrotic. A biopsy was taken and preparation for abdominoperineal resection was begun with administration of chlortetracycline.

The biopsy specimen showed a diffuse granulomatous reaction with many colonies of *E. histolytica* scattered throughout the tissue (Fig. 1). Complement fixation for amebiasis was negative. The white-cell count was 5600 with 86 per cent neutrophils, 10 per cent lymphocytes and 4 per cent eosinophils. Examination of the stools showed no amebas, but these had been done after the patient had received chlortetracycline. A roentgenogram of the chest was normal. Barium-enema study demonstrated rectal narrowing (Fig. 2).

Four days after the institution of chlortetracycline therapy he was almost completely asymptomatic. At that time, on

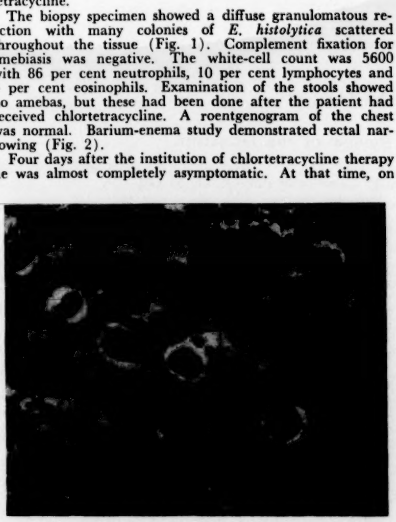


FIGURE 1. *Biopsy of the Rectal Lesion in Case 2, Showing* E. histolytica.

rectal examination, the sphincter tone was normal, there was no incontinence, the annular lesion was much softer and only slightly tender, and the examining finger could be passed through the constriction. Nine days later digital examination of the rectum was negative, and proctoscopic study showed only an irregular area of soft scar. Biopsy of this area disclosed only necrosis and acute inflammation. No amebas were seen.

Chlortetracycline was given for 7 days after which the patient received chloroquine and Diodoquin concurrently. He then received carbarsone. One month after admission he was discharged and was followed periodically as an outpatient. At six months he had remained asymptomatic, and rectal and proctoscopic examinations were normal. Stools were negative for blood, ova and parasites, and the complement fixation for amebiasis was negative.

This patient is an example of an amebic granuloma of the rectum masquerading as a carcinoma. The true nature of the disease was not recognized until the biopsy specimen was examined although the rectal tenderness was unusual. A serious and needless operation was averted, and the patient was cured by medical therapy. It should also be pointed out that this patient acquired his disease in the temperate zone and not in the tropics.

CASE 3. C.A., a 49-year-old American seaman, was admitted to the hospital complaining of diarrhea of 3 or 4 weeks' duration. He was aboard a ship returning from India when he first noticed 2 to 4 watery bowel movements a day. About 1 week before admission the stools became bloody, and he noticed weakness and malaise.

Physical examination disclosed no findings of significance. Proctoscopic study revealed a friable, reddened mucosa, which bled easily.

The white-cell count was 14,400, with 67 per cent neutrophils, 25 per cent lymphocytes, 4 per cent monocytes and 4 per cent eosinophils. Rectal biopsy demonstrated inflammatory changes but no amebas were seen. A stool examination on the day of admission showed bloody mucus but no ova or parasites. Three days after admission cysts of *E. histolytica* were found in a stool specimen. Complement fixation for amebiasis was negative. Barium-enema study of the gastrointestinal tract disclosed marked distortion of the mucosal pattern of the cecum, with deformity of the tip (Fig. 3*A*).

The patient was thought to have either a carcinoma or amebic involvement of the cecum or coexisting amebiasis and carcinoma. It was decided to treat him for amebiasis with fumagillin and to repeat the barium-enema examination. About 1 month after initial roentgenologic studies and the day after the fumagillin therapy had been discontinued, a barium-enema study gave evidence of residual mucosal distortion and irritability of the cecum but no filling defect (Fig. 3*B*). Because he had become asymptomatic and because of the marked improvement on the roentgenogram he was discharged.

He was readmitted to the hospital about 1 month later for abdominal pain and diarrhea of 3 days' duration. Rectal examination was very painful; 3 or 4 cm. from the anus there was a firm annular mass, and just above this lesion

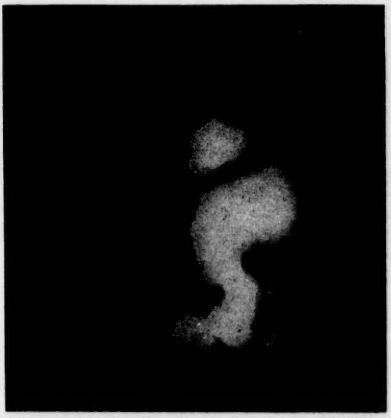


FIGURE 2. *Barium-Enema Examination in Case 2, Showing an Area of Rectal Narrowing.*

there was a firmer, rounded mass. Proctoscopic examination revealed an elevated annular lesion with a dirty-gray surface 4 cm. above the anus. Biopsy of this lesion showed inflammatory tissue, with *E. histolytica* present. Barium-enema study now demonstrated almost complete disappearance of the previous cecal findings. Complement fixation for amebiasis was reported as a doubtful positive. Stool examination disclosed *E. histolytica*.

The patient was given oxytetracycline concurrently with chloroquine. He improved rapidly and later was given Diodoquin and carbarsone. Proctoscopic examination showed progressive healing of the rectal lesions. Forty-six days after the beginning of treatment the rectal mucosa was entirely normal. Complement fixation for amebiasis 1 month after admission was negative.

This patient had two lesions that could easily have been mistaken for neoplasms. On medical therapy

both lesions disappeared completely, and unnecessary surgery was avoided. It is particularly interesting that after initial medical therapy with a single drug one lesion disappeared and a second one developed.

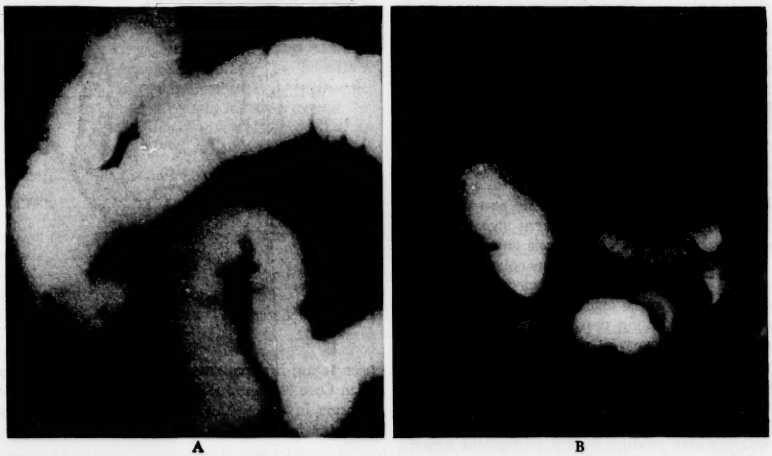
CASE 4. M.P., a 38-year-old Greek seaman, was admitted to the hospital complaining of constant pain in the right lower quadrant of 12 days' duration. Initially, there had been fever and an episode of vomiting and diarrhea.

The only significant finding on physical examination was a tender, well defined firm mass about 4 cm. in diameter in the right lower quadrant. This mass was felt by 7 physicians who examined the patient.

The white-cell count was 8500, with a normal differential. Two stool specimens revealed many cysts of *E. histolytica*. Complement fixation for amebiasis was negative. X-ray study of the chest was within normal limits. Seven days after admission proctosigmoidoscopy to 15 cm. demonstrated no abnormality. Barium-enema examination 11 days after admission showed a constant deformity of the tip and lateral wall of the cecum, apparently caused by their intramural thickening or extrinsic pressure.

Two weeks after admission, even without therapy, the mass was no longer palpable but tenderness persisted in the lower abdomen. At that time simultaneous diodoquin and chloroquine therapy was started, and on completion of this treatment carbarsone was given. Soon after therapy was started the patient became completely asymptomatic.

Barium-enema study 32 days after treatment was started was within normal limits.



A B

FIGURE 3. *Barium-Enema Examination in Case 3 before Treatment* (A), *Showing Changes in the Cecum, and after Treatment* (B), *Showing Great Improvement.*

As in Case 1 there is no histologic proof that the cecal involvement was caused by *E. histolytica*. However, the absence of any other demonstrable etiology and the disappearance of the cecal deformity on antiamebic therapy make the involvement highly likely.

The spontaneous disappearance of the palpable mass within two weeks of admission, even without specific therapy for amebiasis, is an interesting aspect of this case and has previously been reported in the literature.[2,3] An ameboma is not a static lesion and repair and destruction in these cases undoubtedly proceed at different rates in different patients. This patient might have had a spontaneous cure of the amebic infection even without treatment.

HISTORY

As early as 1853 Virchow[4] described inflammatory tumors or pseudo-tumors of the bowel. Since that time Mayo,[5] Moynihan,[6] Mayo-Robson,[7] Hartwell,[8] Kolouch,[9] Lazarus,[10] Walters and Synhorst,[11] and Bargen and Jacobs[12] have reported these inflammatory masses under the guise of such terms as "nontuberculous inflammation of cecum"[8,9] and "ligneous infection of the cecum resulting from subacute appendicitis."[11] Some of these lesions could probably have been proved to be amebic in origin if they had been thoroughly examined.

Although marked thickening of the bowel in amebic infection was noted by Kartulis[13] in 1900 the first clinical case of amebic granuloma was reported in 1916 by Ricaldoni and Berta.[14] Their case involved the cecum and was treated by resection. In 1918, after examining more than 1000 sections of this specimen and a second granuloma of the transverse colon, Lasnier[14] presented his classic paper on the pathology, definitely establishing the lesions as amebic in origin.

In 1924 Montel et al.[15] described, in 10 natives of Annam, right-lower-quadrant masses that disappeared after treatment with emetine. The authors believed that the masses were caused by lymphadenopathy that had followed amebic colitis; however, the patients undoubtedly had amebic granulomas of the cecum. More recently, in numerous scattered reports, such inflammatory masses of the colon have been shown to be amebic either by the presence of organisms in the tissues or by response to medical therapy. Gunn and Howard,[16] in 1931, first suggested the term amebic

granuloma for these inflammatory tumors. In 1939 Ochsner and DeBakey[17] advocated the use of the term ameboma. Many authors have commented on the difficulty of distinguishing these lesions from carcinomas. The need for differential diagnosis and institution of medical therapy is documented by many deaths after operations for amebic granulomas thought to be carcinomas or appendiceal abscesses, and not a few as the result of erroneous diagnosis of inoperable carcinoma and withholding of studies and treatment.

Pathology

The basic pathology is a granulomatous thickening of the colon resulting from necrosis by the amebas, secondary bacterial infection and the cellular and proliferative reaction of the host. Small amebic ulcers limited to the mucosa generally show necrosis without much cellular reaction.[18] When the muscular wall of the bowel is penetrated, however, not only the necrosis but also the cellular response is more extensive, leading to various combinations of fibrosis, granulation and abscess formation. The amebic granuloma may be a well localized lesion involving a small area of the colon or may occupy an extensive part of the large bowel and contiguous areas. The gut wall may be remarkably thickened. Craig[19] has described severe connective-tissue hypertrophy and scarring in chronic amebic colitis that causes the bowel to resemble a rubber hose. Lasnier,[14] in his classic paper in 1918, pointed out three zones of different structure. The inner zone was made up of necrotic tissue containing red and white cells, fibrin and many colonies of *E. histolytica*. The middle zone was formed principally by granulation tissue. The external layer was completely fibrous in the outermost part. These layers varied in width in different parts of the granuloma, and there were superficial and deep abscesses that often communicated with each other, forming "shirt-stud" lesions. It was noted that no amebas were found in the outer zone of the lesion. In treated amebic granuloma the scarring may produce serious, permanent stenosis, but this is unusual.

Incidence

The incidence of the lesion in a given series of cases of amebic colitis varies widely and appears to be less than that of hepatitis and hepatic abscess. Clark[20] noted no amebic granulomas in 186 autopsied cases in which amebiasis was considered the major cause of death. Radke[21] reported 2 granulomas among 96 fatal cases of amebiasis, and Chisholm[22] found 5 in 450 cases of amebiasis. In our own experience there have been 4 cases among 214 patients hospitalized with amebiasis in a period of five and a half years. Since many patients with amebic colitis were treated as outpatients, however, the true incidence is somewhat less. During the same period 14 patients were seen with amebic hepatitis or abscess.

Amebic granulomas occur most commonly in the cecum (Fig. 4).[2,3,14-17,21-111] The rectum, transverse colon, and sigmoid are involved next, in that order of frequency, the rest of the colon being involved only rarely. In 249 autopsied cases of amebiasis summarized by D'Antoni[112] amebic ulcers were found most often in the cecum, rectum and sigmoid, in that order. The transverse colon was found to be least frequently involved. This distribution is similar to that for amebic granuloma.

The granulomas are usually single but may be multiple, the individual lesions being widely separated. Twenty-five cases of multiple tumors are reported in the literature.[22,58-80] As many as 3 distinct lesions have

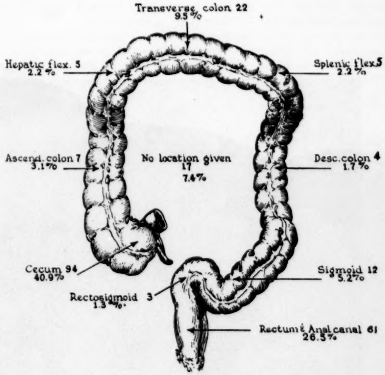


Figure 4. *Location of 230 Amebic Granulomas in 197 Cases.*

been found in 1 patient at the same time.[63,67] Rarely, as in Case 3, a granuloma is found, and later another appears in a different portion of the large intestine after the first has disappeared.[2,76]

Symptoms and Signs

There is nothing specific about the symptoms or physical findings when the colon is involved. The typical patient with a cecal lesion has a bloody diarrhea, right-lower-quadrant pain and a tender mass in the same area. As in any case of amebiasis diarrhea may not occur, or constipation may be present. Fever is not common and when present is usually of low grade. The mass cannot be differentiated from other types of inflammation or a neoplasm arising in the appendix or colon. The rectal granuloma may be indistinguishable from a neoplasm on history and physical examination although palpation is apt to be more painful because of the severe inflammation. On proctoscopic examination the lesion cannot be differentiated from carcinoma of the rectum and is often described as polypoid and ulcerated, with a surface that

bleeds readily. As in the cases reported above, the tumor may be dirty gray or yellowish white and may be covered by a false or diphtheritic membrane. This pseudomembrane may be only in plaques.[81] The lesion may not be as indurated as a carcinoma, but the only certain method of differential diagnosis is biopsy.

Since complications of amebiasis are not uncommon and present the symptoms and signs of the complication, the early history becomes particularly important if unnecessarily extensive surgery is to be avoided and prompt medical therapy for the amebiasis instituted.

Ileocecal intussusception[3,78,82-84] was described in 15 of the 197 reported cases and was the most frequent complication found in review of the literature. Of 13 cases[58,71,75,83,85-93] of intestinal obstruction by an amebic granuloma perforation was seen in only 1.[22] This complication is rare, probably because of the great thickening of the bowel wall caused by the amebic process. Abdominal abscesses,[61,63,72,86,94-96] particularly in the right lower quadrant, may also occur and colonic amebiasis may be complicated by hepatic involvement.[63,86,97] In general, patients with complications sought medical aid because of these events.

Radiologic Findings

Golden and Ducharme[113] have found a recognizable deformity of the cecum on barium-enema study in over a third of their patients with amebiasis. Recognition of cecal deformity by x-ray examination was, in a number of cases, the first suggestion that amebiasis was present. Wilbur and Camp[114] studied 300 barium-enema examinations and found 21 suggestive of amebic disease of the cecum. In 12 of these 21 patients *E. histolytica* was found in the stools. Thirty-seven other patients with amebas in the stools were given barium-enema examinations, and 9 of these showed cecal lesions consistent with amebiasis.

Gunn and Howard[16] state that the x-ray filling defects usually involve such an extensive area that the question of carcinoma does not arise. However, the area of involvement of the colon may be localized and on x-ray examination may be indistinguishable from carcinoma. Druckman and Schorr[98] discuss fully the radiologic differentiation of amebic granuloma and carcinoma. Unfortunately, in many cases only a therapeutic trial with antiamebic drugs or actual biopsy of the lesion will prove the diagnosis. In addition amebiasis and carcinoma of the colon may coexist, making diagnosis virtually impossible until the amebiasis has been adequately treated.

Laboratory Findings

In most cases the stools are positive for *E. histolytica*, but any given patient may not show amebas on repeated examinations. Stempien and Wilkins[67] describe a patient with lesions of the hepatic flexure, transverse colon and cecum in whom twenty-four stool examinations were negative for *E. histolytica* and yet at operation the lesions were found to be amebic in origin. Ash and Spitz[115] state that the failure to find parasites in the stools is not a sound basis for excluding the diagnosis of amebiasis because trophozoites may be absent for long periods and then suddenly appear in showers. On the other hand the presence of amebas in the stools is no guarantee that a colonic mass is not a neoplasm.

In contrast to the positive results obtained in 14 of 15 cases of hepatic abscess and amebic hepatitis by Terry and Bozicevich[116] one must conclude from the limited data available that the complement fixation for amebiasis is negative in most cases. This test, performed by Bozicevich at the National Institutes of Health, was found to be definitely positive in only 1 of our 4 cases. Negative tests are also reported by Perry,[99] Stempien and Wilkins,[67] and Dorset and Spriggs.[86]

Differential Diagnosis

Carcinoma of the colon is the most important lesion that must be distinguished from amebic granuloma. In the literature we have found 31 cases in which carcinoma of the colon accompanied or followed amebiasis.[16,21,61,62,90,100-104,117-125] Thus, the presence of an amebic infection by no means rules out neoplasm. In lesions of the large intestine that are readily accessible to biopsy proof of the diagnosis can usually be obtained. The highest incidence of neoplasm is in the sigmoid and rectum, where biopsy is frequently possible. Often, however, tissue cannot be obtained for histologic study except at laparotomy, which is a dangerous procedure in the presence of an active amebic infection. In 197 cases of ameboma summarized in this paper histologic proof was obtained in only 44. The majority of patients must therefore be treated initially without a definitive diagnosis. Landsman[120] believes that amebiasis and carcinoma occur together much more frequently than is reported because when *E. histolytica* is found in the stools a complete examination of the large intestine is not made. Radke,[21] in a study of autopsy material from 96 cases of amebiasis, found a carcinoma of the colon in 2 and suggested that the amebiasis was an etiologic factor. Reed and Anderson[103] arrived at a similar conclusion on study of 4 cases of carcinoma of the colon that accompanied or followed amebic infection, but this idea remains conjectural at present.

A comprehensive differential diagnosis includes all conditions in which a mass and diarrhea may coexist. The more important are appendiceal abscess, diverticulitis, regional enteritis, tuberculous enteritis, actinomycosis and benign tumor. Absence of amebas from the stools and failure to respond to antiamebic therapy ordinarily make differentiation possible in atypical cases.

Treatment

Surgical

The place of surgery in the treatment of amebiasis is

limited to emergency care of complications, including intussusception, perforation, obstruction and abscess formation. Vigorous medical therapy should be instituted as promptly as possible, and the operation should be very conservative. Resection should be done only as a last resort.

Amebic involvement of skin,[71,89,90,94,105] fulminating exacerbations of the colitis,[86] dangerous hemorrhage[63,96,106] and peritonitis[58,64,86,90,107] are likely to follow surgical intervention. Skin involvement may be accompanied by a fecal fistula or extensive sloughing. Ochsner and DeBakey[17] state that practically every case of invasion of the skin by *E. histolytica* has resulted from surgical or spontaneous drainage of an amebic process; an exception is the perianal region, where amebic lesions of the lower rectum and anal canal may cause skin involvement by direct extension.[17,108,109] Dangerous hemorrhage is seen most frequently from the lesions of cecal amebiasis, according to Hawe.[62] Severe bleeding from the bowel may also occur in patients not operated on. Peritonitis, when it occurs, is often fatal.

The greatest difficulty arises in distinguishing appendicitis or appendiceal abscess from amebic granuloma of the cecum. Cope[106] states:

> The importance of differentiating amoebic (dysenteric) typhlitis from appendicitis is clear, for, while operation in the latter case is urgent, in the former it is dangerous and should be avoided, if possible. . . . in countries where amoebic dysentery is endemic, the surgeon should have the faeces examined and try a short course of emetine before operating on cases with symptoms of appendicitis accompanied by a swelling in the right iliac fossa.

Hawe[62] states that however suggestive of appendicitis an abdominal mass may appear in patients who have lived in endemic areas, before operation is advised an investigation should be undertaken to exclude amebiasis. He adds: . . . "excluding perforation, abscess, and obstruction, there are few exceptions to the rule that operation is strongly contraindicated in intestinal amebiasis." Ochsner and DeBakey[87] believe that, in all chronic inflammatory lesions, particularly those involving the cecum, one should consider the possibility of amebic granuloma, and in the cases in which amebas are found the use of amebicides is imperative before surgical intervention. De Paula and Frota[110] recommend that treatment for amebiasis in patients with this disease be given at the same time as surgery, if surgery is considered urgent. The dangers of surgical intervention have been emphasized by many other authors, especially practitioners in tropical countries. Investigation of the Chicago epidemic of amebic dysentery in 1933 showed that the results of unnecessary surgical interference in these cases was catastrophic.[64] Of 1215 patients studied in this epidemic 77 had operations; 33, or 43 per cent, of these 77 patients died. Appendectomy was a treacherous operation performed in 32 cases, with death in 13, or 41 per cent.

In the 197 cases summarized in this report there were 27 deaths, 21 of which followed surgery. Probably, the death rate is actually higher than these figures indicate because of the tendency for authors to report favorable rather than unfavorable results in any disease.

Occasionally, fibrosis of the colon or rectum sufficient to require surgical correction follows the healing of an ameboma.[43,93,95,122]

Medical

Emetine has been the treatment of choice in most of the reported cases. Nearly all the other antiamebic drugs have been used concurrently or in sequence, with good results. Ochsner and DeBakey[87] describe a patient with an amebic granuloma of the rectum in whom fatal intestinal obstruction developed during treatment with Diodoquin alone. The authors state that these lesions should not be treated with drugs that are effective only in uncomplicated intestinal amebiasis. McVay, Laird and Sprunt[111] used chlortetracycline with good results for postoperative therapy in a patient who had a resection of an amebic granuloma of the transverse colon.

TABLE 1. *Drugs Used in the Treatment of Amebic Granuloma.*

DRUG	DOSE	DURATION OF THERAPY	REMARKS
	gm.	*days*	
Chloroquine (base)	6.9	21	Most useful in extra-intestinal amebiasis
Emetine	0.60—0.72	10—12	Most useful in extra-intestinal amebiasis
Chlortetracycline & oxytetracycline	14.0	7	Probably best when diagnosis cannot be confirmed
Fumagillin	0.42	14	Probably not effective
Diodoquin	37.8	20	Not adequate if used alone
Carbarsone	5.0	10	

Because of the conflicting results reported in the literature in the treatment of amebiasis it is our opinion that no single drug should be used in the treatment of granuloma. In Case 3 the cecal deformity disappeared on fumagillin alone, but the patient returned with an amebic granuloma of the rectum, which responded to oxytetracycline and chloroquine. Case 2 seemed to respond to chlortetracycline alone but was later given other antiamebic drugs. In cases in which a differential diagnosis between amebic granuloma and another inflammatory lesion cannot be made without laparotomy, oxytetracycline or chlortetracycline may be the drug of choice since these antibiotics have antibacterial as well as antiamebic action. Until more is known about the action of the broad-spectrum antibiotics in the treatment of complications of amebiasis it is advisable to use emetine or chloroquine together with the antibiotics. Probably the combination of Diodoquin and chloroquine followed by carbarsone, as in Case 4, is as effective as any other therapy and is much less expensive than antibiotics. Table 1 shows our treatment regimens. In the great majority of cases

reported the lesion disappears within a month of the beginning of treatment.

Conclusions

Amebic granulomas may simulate other inflammatory diseases or neoplasms of the colon. Amebiasis and carcinoma of the colon may coexist.

When a lesion of the colon is inaccessible to biopsy except by laparotomy and an amebic granuloma is suspected a therapeutic trial with antiamebic drugs is indicated before operation is performed.

The great majority of amebomas disappear completely within a month of the beginning of treatment.

Surgical intervention is dangerous in the presence of amebiasis or amebic granulomas and is indicated only for complications. Prompt recognition of the disease at the time of operation and proper therapy often prevent death.

References

1. Anderson, H. H., Bostick, W. L., and Johnstone, H. G. *Amebiasis: Pathology, diagnosis and chemotherapy.* 431 pp. Springfield, Illinois: Thomas, 1953.
2. Case Records of the Massachusetts General Hospital (Case 21312). *New Eng. J. Med.* **213**:235-238, 1935.
3. Ogilvie, W. H. Pitfalls of tropical surgery. *Lancet* **2**:585-587, 1945.
4. Virchow, R. Cited by Silverman and Leslie.[97]
5. Mayo, W. J. Inflammations involving caecum, appendix or both. *Tr. Minnesota State M Soc.* 63-72, 1888.
6. Moynihan, B. G. A. Mimicry of malignant disease in large intestine. *Edinburgh M. J.* **21**:228-236, 1907.
7. Mayo-Robson, A. W. Tumeurs abdominales simulant le cancer et leur traitement. *Gaz. d. hôp.* **131**:483-487, 1908.
8. Hartwell, J. A. Non-tuberculous inflammation of cecum. *S. Clinics North America* **1**:361-365, 1921.
9. Kolouch, F. G. Non-tuberculous inflammation of cecum. *Nebraska M. J.* **8**:106, 1923.
10. Lazarus, J. A. Primary inflammatory tumor of cecum with appendicitis. *Am. J. Surg.* **1**:350-356, 1926.
11. Wetters, W., and Synhorst, A. P. Ligneous infection of cecum resulting from subacute appendicitis. *S. Clin. North America* **6**:1203-1206, 1926.
12. Bargen, J. A., and Jacobs, M. F. Inflammatory cecal tumors: Diagnosis of types of obscure etiology. *Arch. Surg.* **20**:832-850, 1930.
13. Kartulis. In Nothnagel, H. *Specielle Pathologie und Therapie.* 95 pp. Wien: Alfred Hoelder, 1896.
14. Lasnier, E. P. Tumores inflamatorios amebianos del intestino grueso. *An. de la Fac. de med., Montevideo* **3**:809-828, 1918.
15. Monnet, L. R., Trân Van An and Dang Van Cuông. Adenopathies iliaques primitives chez des Annamites de Cochinchine. Guérison par le chlorhydrate d'émétine. *Trop. Dis. Bull.* **21**:470, 1924.
16. Gunn, H., and Howard, N. J. Amebic granulomas of large bowel; their clinical resemblance to carcinoma. *J.A.M.A.* **97**:166-170, 1931.
17. Ochsner, A., and DeBakey, M. Surgical consideration of amebiasis: collective review. *Surg. Gynec. & Obst.* **69**:392-402, 1939.
18. Moore, R. A. *A Textbook of Pathology.* 1338 pp. Philadelphia: Saunders, 1944.
19. Craig, C. F. *Etiology, Diagnosis and Treatment of Amebiasis.* 340 pp. Baltimore: Williams and Wilkins, 1944.
20. Clark, H. C. Distribution and complications of amebic lesions found in 186 post mortem examinations. *Am. J. Trop. Med.* **5**: 157-171, 1925.
21. Radke, R. A. Amebiasis: some features of disease revealed by study of autopsy material from 96 cases. *Gastroenterology* **21**: 525-534, 1952.
22. Chisholm, J. A. Amebiasis. *Rocky Mountain M. J.* **36**:870-878, 1939.
23. Alikishibekov, M. M. Tumor-like amebiasis of large intestine. *Klin. med.* **29**:76, 1951.
24. Paroni, F. Granuloma amebico del ceco. *Ann. radiol. diag.* **22**: 154-161, 1950.
25. Tingaud and Cabanie, H. Sur deux cas de tumeurs caecales d'origine amibienne. *Bordeaux chir.* 46-48, 1950.
26. Broide, L. Granuloma amibiano de colon. *Prensa méd. argent.* **37**: 823-834, 1950.
27. Prat D. Síndrome apendicular con tumefacción ulcerada del ciego por posible amebiasis. *Arch. urug. de med., cir. y especialid.* **23**: 125-127, 1943.
28. De Oliveira, E. Amebic granuloma simulating rectal cancer with report of cases. *Rev. de gastro-enterol. de São Paulo* **4**:189-193, 1941.
29. Amalfitano, G. Pseudocancro del ceco di origine amebica. *Trop. Dis. Bull.* **44**:902, 1947.
30. Brugeas. Sur un début de dysenterie à forme appendiculaire. *Trop. Dis. Bull.* **19**:691, 1922.
31. Cropper, C. F. J. Amoeboma of the hepatic flexure. *Brit. M. J.* **1**:988, 1946.
32. Desjardins, A. Les pseudo-cancers coliques d'origine amibienne. *Bull. et mém. Soc. de chir. de Paris* **21**:443-452, 1929.
33. Donoso, I. A., and Amenabar, C. E. Pseudo-canceres rectales de origen amebiano (granuloma amebiano). *Rev. méd. Chile* **80**: 236-240, 1952.
34. Dor, J., and Vague, J. Pseudo-cancer rectal volumineux d'origine amibienne, disparaissant en quelques jours sous l'effet de l'émétine. *Arch. d. mal. de l'app. digestif* **37**:618, 1948.
35. Furuichi, T. On perityphlitis caused by dysentery ameba. *Trop. Dis. Bull.* **19**:328, 1922.
36. Gandolfo-Canessa, J. A. Image pseudo-tumorale en cocarde par oedème de la valvule de Bauhin au cours d'une typhlite amibienne. *Arch. d. mal. de l'app. digestif* **39**:821-823, 1950.
37. Guichard and Paponnet. Pseudo-cancer recto-sigmoïdien d'origine amibienne. *Arch. d. mal. de l'app. digestif* **25**:450-459, 1935.
38. Hargreaves, W. H. Chronic amoebic dysentery: new approach to treatment. *Lancet* **2**:68-72, 1945.
39. Hawe, P. Amoeboma and carcinoma. *Lancet* **2**:508, 1946.
40. Hummel, H. G. Amebic granuloma of rectum and balantidiasis in same patient. *Am. J. Digest. Dis.* **7**:178, 1940.
41. Ibarbia, F. D. Granuloma inflamatorio del ciego de origen amebiano. *Rev. med.-social san. y benef. munic.* **6**:38-41, 1946.
42. Lindskog, G. E., and Walters, W. Surgical aspects of amebic dysentery. *J.A.M.A.* **131**:92-95, 1946.
43. Mendelson, R. W. Surgical manifestations of amebiasis. *Southwestern Med.* **23**:361-366, 1939.
44. Molinier, A., Bensaude, A., and Tabusse. Les lésions rectales de la dysenterie amibienne. *Arch. d. mal. de l'app. digestif* **38**:331-337, 1949.
45. Montel, G. H. M., and Montel, M. L. R. Un nouveau cas d'adénopathy iliaque d'origine problement amibienne. *Trop. Dis. Bull.* **22**:346, 1925.
46. Montel, M. L. Les amaebomes tuméfactions ileo-caeco-coliques pseudo-tumorales avec adénopathies mésentériques et iliaques dues à l'amibiase. *Trop. Dis. Bull.* **47**:39-49, 1950.
47. Moreno, N. W., and Wasserman, I. F. Tumor amibiano rectal: disenteria cronica. *Arch. argent. de enferm. d. ap. digest. y de la nutrición* **17**:449-456, 1942.
48. Niño, F. L. Tumores inflamatorios amibianos del intestino grueso. *Trop. Dis. Bull.* **40**:145, 1943.
49. Nushan, H., and Miller, B. Ameboma of transverse colon. *Ann. Int. Med.* **37**:372-379, 1952.
50. Read, W. A., and Nushan, H. Amebic granuloma (ameboma) simulating carcinoma. *Gastroenterology* **15**:771-779, 1950.
51. Rogers, L. *Recent Advances in Tropical Medicine.* 406 pp. Philadelphia: Blakiston, 1929.
52. Runyan, R. W., and Herrick, A. B. Surgical complications and treatment of intestinal amebiasis. *Am. J. Trop. Med.* **5**:137-147, 1925.
53. Smith, S. L. H., and Clow, J. M. Importance of amebioma in differential diagnosis of abdominal swellings. *Chinese M. J.* **67**: 193-195, 1949.
54. Spiesman, M. G. Discussion of Silverman, D. N., and Leslie, A. Intractable amebic colitis. *J.A.M.A.* **129**:190, 1945.
55. Timbal and Auriol. Un nouveau cas de pseudo-cancer recto-sigmoïdien d'origine amibienne. *Arch. d. mal. de l'app. digestif* **27**:989, 1947.
56. Uzac and Timbal. Pseudo-cancer recto-sigmoïdien d'origine amibienne. *Arch. d. mal. de l'app. digestif.* **27**:986-988, 1937.
57. Donald, C. J., Jr., and Brown, P. W. Amebic granuloma simulating carcinoma of rectum. *Proc. Staff Meet., Mayo Clin.* **15**:321-323, 1940.
58. Likely, D. S., and Lisa, J. R. Granuloma of large intestine associated with amebiasis. *New York State J. Med.* **42**:2322, 1942.
59. Harrison, W. F. Histopathology of appendiceal amebiasis with case report. *Ann. Int. Med.* **2**:1081-1091, 1929.
60. James, W. M., and Deeks, W. E. Etiology, symptomatology and treatment of intestinal amebiasis. *Am. J. Trop. Med.* **5**:97-136, 1925.
61. Kleitsch, W. P., and Cherry, L. D. Surgical importance of amebiasis. *Mil. Surgeon* **105**:458-466, 1949.
62. Hawe, P. Surgical aspect of intestinal amebiasis. *Surg., Gynec. & Obst.* **81**:387-404, 1945.
63. Lund, C. C., and Ingham, T. R. Four fatal cases of unsuspected amebiasis; preliminary report on one aspect of recent Chicago epidemic. *J.A.M.A.* **101**:1720-1722, 1933.
64. *Epidemic Amebic Dysentery: The Chicago outbreak of 1933. (National Institute of Health Bulletin 166.)* Washington: Government Printing Office, 1936.
65. Lambret. Pseudo-cancer inflammatoire du côlon transverse. *Congrès français de chirurgie* **19**:185-188, 1906.
66. Augé, A., and Viennot-Bourgin. Côlite amibienne à forme pseudo-tuberculeuse. *Arch. d. mal. de l'app. digestif* **25**:857-861, 1935.
67. Stempien, J., and Wilkins, F. P. Amebiasis of colon simulating obstructing carcinoma. *Gastroenterology* **16**:598-601, 1950.
68. Zucker, G. Amebic granuloma of cecum. *Rev. Gastroenterol.* **14**:609-613, 1947.
69. Stark, W. Seltene Faelle Chronisch-Entzuendlicher Tumoren des Dickdarms. *Med. Welt* **1**:602-604, 1927.
70. Rudolph, A. M., and Braudo, J. L. Ameboma of large bowel with review of literature. *Clin. Proc.* **6**:287-291, 1947.
71. Cameron, J. A. M., and Collins, J. C. Intestinal obstruction by amebic granulomata. *J. Roy. Army M. Corps* **79**:140-142, 1942.
72. Karlen, M. A. Un nuevo caso de tumor inflamatorio amibiano de Lasnier. *Bol. Soc. cir. d. Uruguay* **14**:17-26, 1943.
73. Niño, F. L. Amebiasis intestinal ulcero-necrótica y tumor amebiano del ciego y colon ascendente. *Novena Reunión Soc. Argent. de Pat. Reg.* **2**:813-843, 1937.
74. Pia, J. C., and Munoz Monteavaro, C. Amibioma del colon: enfermedad de Gamonara y Lasnier. *Arch. urug. med.* **35**:1-15, 1949.
75. Yeomans, F. C. Amebic granuloma simulating carcinoma of colon and rectum. *Am. J. Surg.* **31**:365, 1936.
76. Finochietto, E., and Vaccarezza, R. F. Tumor inflamatorio del intestino grueso de origen amibiano. *Trop. Dis. Bull.* **19**:28, 1922.
77. Nevin, R. W. Amoebic granuloma. *Proc. Roy. Soc. Med.* **42**:769-774, 1949.
78. Reddy, D. G., and Rangam, C. M. Amoebic granuloma (amoeboma) of large intestine. *Indian M. Gaz.* **81**:463-466, 1946.
79. Coumel, Molinier, Duchesne and La Peyre. Les rétrécissements recto-colique de l'amibiase. *Arch. d. mal. de l'app. digestif* **39**: 1278-1284, 1950.
80. Rachet, J., Busson, A., and Arnons-Joudre, J. Tumeur inflammatoire amibienne simulant un cancer du côlon transverse. *Arch. d. mal. de l'app. digestif* **37**:631, 1948.

81. Bocca, C. R. La forme pseudo-cancereuse de l'amibiase recto-sigmoïdienne. *Gaz. méd. de France* **23**:5, 1939.
82. Iriart, M., and Colombo, E. Invaginación intestinal en el adulto tumor amebiano del ciego. *Dia. méd.* **16**:1190-1198, 1944.
83. Theron, P. Surgical aspects of amoebiasis. *Brit. M. J.* **2**:123-126, 1947.
84. Huard, P. Nouvelles recherches sur les aspects chirugicaux des dysenteries et colites tropicales. *Arch. d. mal. de l'app. digestif* **27**:473-518, 1937.
85. Rivas, D. B. Obstrucción intestinal por tumor inflamatorio amebiano. *Bol. y trab., Acad. argent. cir.* **35**:185, 1951.
86. Dorset, V. J. and Spriggs, J. B. Diagnostic difficulties relating to amebiasis with 5 case reports. *Ann. Int. Med.* **36**:1459-1466, 1952.
87. Ochsner, A., and DeBakey, M. Surgical amebiasis. *Internat. Clin.* **1**:68-99, 1942.
88. Rachet, J. A propos de quelques formes anormales d'amibiase intestinale. *Paris méd.* **1**:341-346, 1929.
89. Bassler, A. Intestinal obstruction due to amebiasis. *J.A.M.A.* **106**: 1965-1968, 1936.
90. Gatewood. Surgery in amebiasis. *Illinois M. J.* **71**:41-45, 1937.
91. Goyena, J. R. Obstrucción intestinal por recto-sigmoiditis y peri-sigmoiditis supurada de origen amebiano. *Semana méd.* **31**:10-14, 1924.
92. Harán, A. M. Oclusión intestinal por tumor cólico amibiano. *Arch. urug. de med. cir. y especialid.* **16**:177, 1940.
93. Morton, T. C. Diagnosis of chronic dysentery in service personnel: analysis of 100 sigmoidoscopies. *Brit. M. J.* **2**:890-893, 1946.
94. Cox, A. L., and Achuton. Case of amoeboma with abscess formation followed by infection of drainage wound. *Indian M. Gaz.* **82**: 536-538, 1947.
95. Christopher, F. Stenosis of large bowel due to amebiasis; report of case treated by extensive resection. *Surgery* **3**:75-77, 1938.
96. Ernst, K. F. Amebic granuloma simulating carcinoma. *U. S. Armed Forces M. J.* **4**:1069-1076, 1953.
97. Silverman, D. N., and Leslie, A. Intestinal tumors of dysenteric origin. *J.A.M.A.* **133**:994-998, 1947.
98. Druckman, A., and Schorr, S. Roentgenological manifestations of amebiasis of large intestine. *Am. J. Roentgenol.* **54**:145-148, 1945.
99. Perry, M. W. Amebic granuloma of rectum. *J.A.M.A.* **148**:369, 1952.
100. Bell, J. C. Roentgenologic studies of large bowel in infections by *Endamoeba histolytica* before, during and after treatment. *Am. J. Roentgenol.* **39**:916-924, 1938.
101. Cade, A., and Milhaud, M. Amibiase et cancer du gros intestin. *J. de méd. de Lyon* **20**:475-479, 1939.
102. Huard, P. Aspects chirugicaux de l'amibiase coeco-colique. *Marseille-méd.* **2**:549-585, 1933.
103. Reed, A. C., and Anderson, H. H. Amebiasis and cancer of colon. *Am. J. M. Sc.* **191**:237-250, 1936.
104. Sodeman, W. A., and Engle, P. R. Amebic granuloma of colon. *Am. J. Digest. Dis.* **19**:363-367, 1952.
105. Smyth, M. J. Confusion of amoeboma with carcinoma. *Lancet* **2**: 376, 1946.
106. Cope, V. Z. *Surgical Aspects of Dysentery Including Liver-Abscess.* 157 pp. London: Frowde, Hodder and Stoughton, 1920.
107. Solé, R., and Bacigalupo, J. Tumor inflamatorio paraintestinal de origen amibiano. *Arch. argent. de enferm. d. ap. digest. y de la nutrición* **1**:412-429, 1926.
108. Howells, G. Two cases of amoebic granuloma. *Brit. M. J.* **1**: 161, 1946.
109. Lee, R. S. H. Amebic granuloma simulating epithelioma of anus. *Trop. Dis. Bull.* **39**:317, 1942.
110. De Paula, H. V., and Frota, P. Surgical aspects of protozoal infections. *Trop. Dis. Bull.* **39**:315, 1942.
111. McVay, L. V., Jr., Laird, R. L., and Sprunt, D. H. Treatment of amebiasis with aureomycin. *South. M. J.* **43**:308-313, 1950.
112. D'Antoni, J. S. Amebiasis: recent concepts of its prevalence, symptomatology, diagnosis and treatment. *New Internat. Clin.* **1**: 100-108, 1942.
113. Golden, R., and Ducharme, P. Clinical significance of deformity of cecum in amebiasis. *Radiology* **45**:565-580, 1945.
114. Wilbur, D. L., and Camp, J. D. Amebic disease of cecum: clinical and radiologic aspects. *Gastroenterology* **7**:535-548, 1946.
115. Ash, J. E., and Spitz, S. *Pathology of Tropical Diseases: An atlas.* 350 pp. Philadelphia: Saunders, 1945.
116. Terry, L. L., and Bozicevich, J. Importance of complement fixation test in amebic hepatitis and liver abscess. *South. M. J.* **41**: 691-702, 1948.
117. Chaudhuri, R. N., and Chakravarty, H. Case of carcinoma of colon with amebic infection. *Indian M. Gaz.* **81**:422, 1946.
118. Chiray, M., and Dupuy, R. Cancer du rectum sur terrain amibien. *Semaine d. hôp. de Paris* **27**:2824-2826, 1951.
119. Girault, A., and Mariani, R. Amibiase et cancer rectosigmoïdien. *Arch. d. mal. de l'app. digestif* **28**:380-383, 1938.
120. Landsman, A. A. Amebic dysentery as complication of carcinoma of rectum. *New York State J. Med.* **41**:1181, 1941.
121. Bargen, J. A. Amebiasis associated with carcinoma. *Am. J. Digest. Dis. & Nutrition* **3**:268, 1936.
122. Morgan, C. N. Amebiasis: some difficulties in diagnosis. *Brit. M. J.* **2**:721, 1944.
123. Moutier, F., and Brousse, P. Dysenterie amibienne et cancer du rectum. *Presse therm. et climat.* **85**:683-685, 1924.
124. Raúl Goyena, J. Cancer del recto y amibiasis. *Trop. Dis. Bull.* **25**:219, 1928.
125. Roux, J. C., and Savignac, R. Dysenterie amibienne et cancer du rectum. *Arch. d. mal. de l'app. digestif* **17**:199-208, 1927.

MECHANISMS OF WOUND HEALING*

Comparison of Preliminary Local and Distant Incisions

EDWIN D. SAVLOV, M.D.,† AND J. ENGLEBERT DUNPHY, M.D.‡

BOSTON

THE presence of a factor promoting the rehealing of wounds has been postulated for many years. The excellent healing of the resutured dehiscence has often been noted clinically.[1] However, evidence of the nature of the factor or factors responsible for this effect has been lacking.

A systemic healing-promoting factor was proposed by Sandblom[2] as being responsible for the increased rate of healing that he found in wounds made after a given time at a distance from a primary wound. The greatest effect seemed to be present during the second week after wounding. This concept has been disputed by Taffel, Donovan and Lapinski.[3]

Reports by Botsford[4] and Williams et al.[5] indicate that the gain in strength of a resutured wound is regularly greater than the rate of gain of the primary wound. Possible factors involved in such an effect may be as follows: the continuation of the local process of fibroblastic regeneration after resuturing without the necessity for return to the initial phase of demolition and defense characterizing the "lag phase"; or the progression of systemic effects set in motion by the primary stress of wounding. With the recent increase in knowledge of the metabolic responses to stress[6] further studies of the relation of wound healing and systemic responses seem justified.

The present study is the initial phase of an analysis of the role of systemic and local factors in the process of wound healing.

METHOD

A method for the measurement of the tensile strength of abdominal wounds in rats in vivo was devised, based roughly on the procedure of Williams, Mason and Bradshaw.[5]

*From the Surgical Service, Peter Bent Brigham Hospital, and the Department of Surgery, Harvard Medical School.

Financed in part by United States Public Health Service Grant RG-1600.

†Public Health Service research fellow of the National Cancer Institute, Harvard Medical School; assistant in surgery, Peter Bent Brigham Hospital.

‡Clinical professor of surgery, Harvard Medical School; surgeon, Peter Bent Brigham Hospital.

Under ether anesthesia a 4-cm. left-rectus-muscle incision is made. While the abdomen is open two small No. 32 stainless-steel wire loops are placed through the abdominal wall 1 cm. lateral to the wound on each side. Inside the abdomen these loops pass

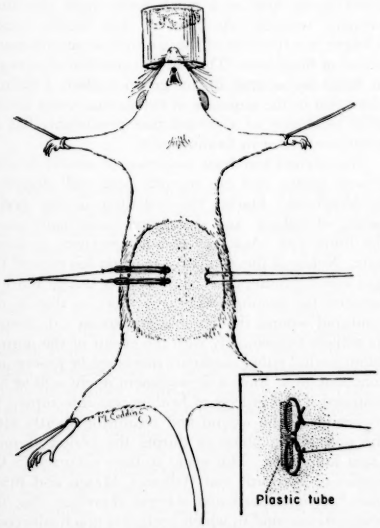


FIGURE 1. *Technic of Disrupting an Abdominal Wound in the Rat.*

At the time of the initial laparotomy two wire loops are placed 1 cm. laterally on each side of the wound. They are passed through a fine polyethylene tube intraperitoneally (insert) to prevent the wires from pulling through the abdominal wall when tension is applied. Safety pins are attached on one side of the wound while a loop of fish line is passed through the pull wires on the other side. At any time desired the wound can be disrupted by graded traction on the wire loops, as described in the text.

through a fine polyethylene tube, 8 mm. in length, running parallel to the incision, which prevents the wires from pulling through the tissue and distributes the pull more evenly over the length of the wound. (See insert in Figure 1.) These "pull wires" are left in place throughout the experiment. The wound is then closed with interrupted No. 32 stainless-steel through-and-through sutures.

When the wound is to be tested the animal is anesthetized, the sutures are carefully removed, and one side of the wound is attached through the "pull wires" to a fixed pole. The opposite "pull wires" are attached by a fish line to a light plastic bag suspended over a pulley. Increasing tension on the wound is caused by water flowing at a steady rate into the plastic bag. The weight of the bag and the water at the time of complete separation of the abdominal wall is taken as the disruption strength. The wound can then be resutured for further studies.

Repeated studies revealed that by this method the mean rupture tension of a three-day wound in 38 rats was 122 gm. with a variation in individual animals from a low of 0 to as high as 253 gm. The standard deviation of the group was ±60 gm.

PROCEDURE

Forty-eight male Hisaw rats weighing between 180 and 250 gm. were selected at random and divided into three equal groups. All were maintained on the same diet of Purina laboratory chow with water ad libitum. The groups were treated according to the schedule presented in Table 1.

TABLE 1. *Schedule of Wounds.*

GROUP	FIRST DAY	SIXTEENTH DAY	NINETEENTH DAY
Controls	No wound	Abdominal incision	
Group 1	Deep back wound, through skin & muscle	Abdominal incision	Tensile strengths of all abdominal incisions tested
Group 2	Abdominal incision	Previous incision reincised & resutured	

All wounds were made after shaving of the operative area, sterile technic being used. Several animals died during anesthesia and are not included in the results.

TABLE 2. *Results of Wound Testing.*

TENSILE STRENGTH CONTROLS gm.	TENSILE STRENGTH GROUP 1 gm.	TENSILE STRENGTH GROUP 2 gm.
149	250	413
148	133	483
189	123	385
114	123	460
139	313	350
215	173	397
103	200	325
43	185	417
243	145	354
176	190	358
23	90	453
95	240	253
193	95	301
23		253
253		353
73		
Mean 141±74*	176±66*	378±70*

*Standard deviation derived from the formula $S_x = \sqrt{\frac{\Sigma(x-\bar{x})2}{n-1}}$

As seen in Table 2 and as graphically illustrated (Fig. 2) the strength of the three-day abdominal wound in the previously unwounded animals closely approximated that of the abdominal wounds in the animals wounded on the back fifteen days previously. On the other hand the abdominal wounds that had been opened on the fifteenth postoperative day and resutured were consistently and considerably stronger than the others. A statistically significant difference

exists between the figures for Group 2 and those for the other groups.

Under the conditions of this experiment there is no evidence to support the report of Sandblom[2] that a wound previously made elsewhere in the body promotes more rapid healing of a second incision. Although no significant difference in bursting pressures of the wounds in Group 1 and Group 2 could be demonstrated we thought that the slight difference in mean values might indicate a minimal effect that could be brought out more clearly by multiple wounding. This possibility was investigated. Ten rats were wounded on the back. Fifteen days later a second

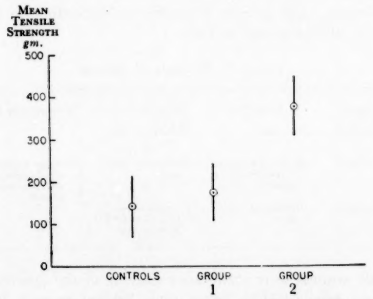


FIGURE 2. *Mean Tensile Strength and Standard Deviation of the Three Experimental Groups.*

The control group had only an abdominal wound, which was tested on the third day. Group 1 was treated similarly except that a deep back wound had been inflicted fifteen days before the abdominal wound. In Group 2 an abdominal wound was made and then opened and resutured after fifteen days and tested three days later.

wound on the back on the opposite side was made, and after a lapse of fifteen more days a standard abdominal incision was made and tested three days later. The average tensile strength of these abdominal wounds was 143 gm., no different from that in our control group and indeed somewhat less, suggesting the possibility that the stress of the two incisions, if anything, impaired rather than promoted the rate of healing.

Discussion

Our findings are in accord with the work of Taffel et al.,[3] who also could not demonstrate a favorable effect of one wound on another. They used as a test the fifth-day bursting pressure of a wound in the stomach of a rat produced fifteen days after a wound on the back in the same animal. An increased tensile strength on the fifth day might be due to an early onset of fibroplasia, which then proceeded at a normal rate, or an increased rate of fibroplasia after a normal latent period. We have preferred, therefore, to use the bursting pressure of a third-day wound, believing that an increase in tensile strength at this time would indicate a definite shortening of the lag period rather than an increased rate of fibroplasia.

It is of interest, however, that whereas no evidence of a favorable effect of a wound made at some other site in the body on a second wound could be demonstrated, fifteen-day-old wounds, if reopened and sutured again, heal at a much more rapid rate than primary wounds. As Harvey[7] has stated, tensile strength is a function of the multiplication and maturation of fibroblasts. The rapid acquisition of strength in three-day wounds in this group suggests a definite alteration in the sequence of events that occur locally after resuturing of a wound that presumably has already completed its healing cycle.

The normal histologic sequence of wound healing is well known and has recently been well described by Needham.[8] During the first three to five days a period of defense and demolition takes place under the fibrin clot. Autolysis and phagocytosis predominate. Not until this exudative reaction has cleared the way can a proliferation of fibroblasts bridge the gap between the healing surfaces. It may be that in the resutured wound the fibroblastic process can resume its activity immediately with the events of the normal latent period either markedly shortened or proceeding concomitantly. Such a development might well be anticipated if the process of healing was interrupted by reopening of the wound and resuturing shortly after the normal lag phase or during the period of most rapid fibroplasia. This seems to have occurred in the studies of Botsford[4] and Williams, Mason and Bradshaw.[5] It is of particular interest, therefore, that the fifteen-day wound in which healing is practically complete should also show this ability to heal at a more rapid rate than the normal wound.

Further investigations of this phenomenon are in progress. One of the features of the healing of secondary wounds that has not been sufficiently elaborated is the structure of the total curve of healing in the resutured wound. A number of studies have shown an increased tensile strength at various periods, but it has not yet been adequately demonstrated that these wounds attain their full strength at a more rapid rate than normal wounds.

Summary

Wounds of the abdomen made fifteen days after wounds on the back in rats did not show any greater tensile strength on the third day than three-day abdominal wounds of a control group on which no previous wounding had been made. A summation of such an effect could not be demonstrated by multiple wounding on the back before an abdominal wound.

Fifteen-day-old abdominal wounds that were opened and resutured revealed a significant increase in tensile strength on the third day after resuture.

References

1. Hartzell, J. B., and Winfield, J. M. Disruption of abdominal wounds: collective review. *Internat. Abstr. Surg.* 68:585-601, 1939.

2. Sandblom, P. Effect of injury on wound healing. *Ann. Surg.* **129**: 305-314, 1949.
3. Taffel, M., Donovan, A. J., and Lapinski, L. S. Effect of trauma on wound healing: experimental study. *Yale J. Biol. & Med.* **23**: 482-485, 1951.
4. Botsford, T. W. Tensile strength of sutured skin wounds during healing. *Surg. Gynec. & Obst.* **72**:690-697, 1941.
5. Williams, R. W., Mason, L. B., and Bradshaw, H. H. Factors affecting wound healing. *S. Forum* (1950). Pp. 410-417, 1951.
6. Moore, F. D. Bodily changes in surgical convalescence. I. Normal sequence — observations and interpretations. *Ann. Surg.* **137**:289-315, 1953.
7. Harvey, S. C. Velocity of growth of fibroblasts in healing wound. *Arch. Surg.* **18**:1227-1240, 1929.
8. Needham, A. E. *Regeneration and Wound Healing*. 152 pp. New York: John Wiley and Sons, 1952. Pp. 3-23.

PROGERIA*

Report of a Case with Post-Mortem Findings

LEONARD ATKINS, M.D.†

BOSTON

SINCE the original description of cases of progeria by Hutchinson[1] in 1886 and Gilford[2] in 1897 only 22 such cases have been reported. Children with this syndrome show a striking resemblance to each other. They appear normal at birth, dwarfism being noted within the first few years of life. Associated with dwarfism is a typical facies with a beaklike nose, a relatively small face with receding chin, exophthalmos, loss of hair, prominent scalp veins, markedly diminished subcutaneous fat, muscular atrophy, arthritic joint deformities, shortened clavicles, coxa valga, a "horse-riding" stance, arteriosclerosis and normal or above normal intelligence for the patient's age. Such patients usually fail to survive adolescence and succumb to coronary-artery disease. The oldest, described by Manschot,[3,4] died at the age of twenty-seven. There is no familial incidence of the disease, nor is there any predilection for either sex. Other cases, classified as progeroid, have many features in common with classic cases, but the complete, characteristic picture is lacking. Thomson and Forfar[5] found 18 classic cases in the literature up to 1950 and added 1 of their own. Autopsies have been performed in only 4 cases. Since 1950 3 additional cases have been described but without post-mortem data.[6-8] The present case is the twenty-third reported case, the fifth with a post-mortem examination and the second from this hospital. That this is a classic example of the disease can be ascertained from the following data and the accompanying illustration (Fig. 1).

CASE REPORT

E.R. (M.G.H. 422606) was the 2d of 3 children of parents of Italian extraction. Both parents and siblings were healthy. He was a full term male infant weighing 3.1 kg. at birth. Delivery was normal. Shortly after birth it was noted that his abdomen was covered by thick and irregularly pigmented skin. In spite of a seemingly adequate dietary intake he weighed only 3.4 kg. at 6 months, 4.5 kg. at 1 year and 7 kg. at 2 years of age. At about 1 year of age he had occasional vomiting after meals for a few months. It was noted that he sweated a good deal at night. He walked at 1 year and talked at 18 months. The 1st teeth erupted at 14 months. He was seen in the clinic at 17 months because of a traumatic hematoma of the forehead. No obvious signs of the disease were present at this time. He had chicken pox at 19 months. Because of slow weight gain, unusual facies and the skin condition previously noted he was brought to the hospital at the age of 2 10/12 years.

Physical examination showed a striking appearance. Although he was of normal size for his age the head appeared large, with prominent scalp veins, protruding eyes and a slightly receding lower jaw (Fig. 1). He weighed 8.2 kg. The circumference of the head was 47.6 cm., that of the chest 43.2 cm., and that of the abdomen 40 cm. The anterior fontanelle was open. Four lower incisor, 3 upper central incisor and 2 upper molar teeth were present. The skin of the abdomen was thick and somewhat pitted, with some brown pigmentation. The testes were descended. There was a 30° limitation of flexion of both wrists and a 40° limitation of flexion of both knees. A systolic bruit was heard over the right frontoparietal area, maximally over the anterior fontanelle. The heart was not enlarged, and the cardiac rhythm was regular. A soft systolic murmur was heard over the apex and the base. The blood pressure was 90/50. The liver and spleen were not palpable.

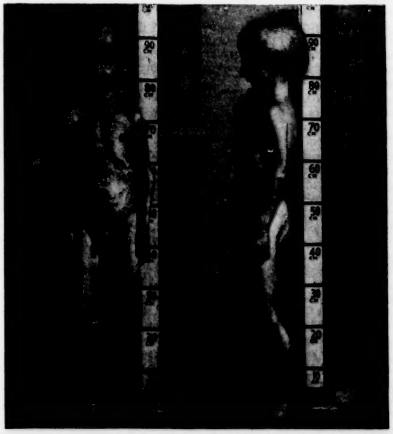


FIGURE 1. *Appearance of the Patient at the Age of Eight Years and Five Months.*

The hemoglobin and white-cell count were normal. The serum calcium was 11.7 mg., the serum phosphorus 2.4 mg., and the alkaline phosphatase was 4.8 Bodansky units per 100 cc. Insensible weight loss, which was unusually high, was 1900 cc. per square meter per 24 hours (normal, about

*From the Department of Pathology, Massachusetts General Hospital.
†Assistant resident in pathology, Massachusetts General Hospital.

1000 cc. per square meter per 24 hours). X-ray studies showed a bone age corresponding to the chronologic age. Epiphyseal development appeared to be quite normal. There was no evidence of demineralization. No enlargement of the sella turcica was seen. The clinoid processes were well developed and appeared normal. Shortening of the clavicles was noted. In later films the bones were described as delicate, being rather narrow but of normal osseous structure. Coxa valga was also seen. Injection of the right internal carotid artery with Diodrast showed a normal-sized vessel with normal anterior and middle branches. The veins were also normally visualized as far as could be determined. Insulin and glucose tolerance tests, as well as an electrocardiogram, were interpreted as normal. An electroencephalogram showed frequencies that were normal for the subject and also frequencies that were slower than normal. Biopsy of the skin of the abdomen demonstrated scleroderma, with marked fibrosis of the corium; there was some melanin pigmentation of the basal layer of the epithelium.

The patient was subsequently followed over a period of years and numerous studies were carried out. The physical features previously described gradually became more prominent and progressed to the full-blown classic picture of a prematurely old, wizened person. The anterior fontanelle remained open, and the head seemed larger; the systolic bruit over the right frontoparietal area persisted, and the hair became sparse. There was malocclusion and crowding of the teeth. Arthritic deformities developed, with increasing limitation of mobility in the wrists, knees and finger joints. The voice became high pitched and squeaky. There was a progressive loss of subcutaneous tissue. With an increase in dietary intake he gained weight, but it was almost impossible to increase his calories for more than a few days without inducing nausea. He weighed 8 kg. at 3½ years, 8.8 kg. at 5 years, 10.2 kg. at 6½ years, 9.3 kg. at 8 4/12 years and 10.2 kg. at 10 years of age. His height at 5 years was 83.8 cm., and at 10 years it was 96.5 cm.

A 6-month course of thiouracil was given at the age of 3 because of an elevated metabolic rate as evidenced by the high, insensible weight loss; this was without effect except for moderate thyroid enlargement and bruit over the gland. Methyl testosterone produced an increase in the muscle mass at the expense of subcutaneous tissue. The metabolic processes did not appear to be affected by chlorobutanol or vitamin E.

At the age of 5 the cardiac systolic murmur was described as somewhat harsh and transmitted to the left axilla. The blood pressure was 90/60. At the age of 8 5/12 years a soft apical systolic blow was described as well as a loud apical 3d sound. The blood pressure was then 125/80. Numerous electrocardiograms were all within normal limits.

Examination of the blood at various times revealed a serum calcium of 9.2 to 10.1 mg., serum phosphorus of 5.3 mg., alkaline phosphatase of 4.7 and 3.4 Bodansky units, serum cholesterol of 287, 258, 240 and 264 mg. and total serum protein of 7.5 gm. per 100 cc. A 24-hour urine sample obtained at the age of 8½ contained 0.54 gm. of creatinine and 0.8 gm. of creatine. The creatinine coefficient was 58 gm. per kilogram of body weight; 17-ketosteroid determinations were 1.5 mg. and 0.8 mg. per 24 hours. Vital capacity was 500 cc. Psychometric studies done at 4½ years showed average intelligence for this age.

Except for mumps at 3 2/12, an episode of cervical adenitis at 5 7/12 and measles at 6 4/12 years of age, as well as several upper respiratory infections and traumatic accidents, the patient remained in relatively good health until about the age of 9 when he had 1 or 2 episodes each month of severe frontal headaches associated with dizziness and nausea over a period of 1 year. At 9 10/12 years he was admitted to the hospital with a 2-week history of attacks of nocturnal dyspnea. The blood pressure was 92/50. Examination of the heart showed the point of maximal impulse to be 1 cm. lateral to the midclavicular line in the 5th left interspace. Heart sounds were loud, and there was a sinus tachycardia (rate of 108 per minute), with a protodiastolic gallop rhythm. A short, harsh Grade 2 systolic murmur was heard at the apex. X-ray study of the chest demonstrated the cardiac shadow to be at the upper limits of normal size. Ophthalmoscopic examination disclosed arteriolar narrowing and tortuosity, with slight arteriovenous nicking. He was digitalized, and the pulse rate fell to normal. The gallop rhythm disappeared, and the nocturnal dyspnea was relieved. He was placed on a maintenance dose of digitoxin, and 10 mg. of ACTH was given every 6 hours for 7 days, with some improvement in the mobility of the elbows and ankles and a drop in the eosinophil count to 0. An electrocardiogram was interpreted as showing a probably old anteroseptal myocardial infarction. About 11 hours after ACTH therapy had been discontinued the patient complained of a severe bitemporal headache, and the blood pressure was noted to be 220/130. With sedation the blood pressure gradually dropped to 120/80 over the next 2 days. Two weeks later it was 150/110. No subsequent blood pressures were recorded.

For the last 2 years of his life his activity was restricted. He had been taking digitalis irregularly. The final admission was at the age of 11 3/12 years because of chest and abdominal pain. For 2 nights nocturnal dyspnea had become increasingly frequent. On admission he was in shock, with an unobtainable blood pressure, and in severe congestive heart failure. An electrocardiogram was consistent with an acute anterior myocardial infarction. He died about 8½ hours later.

Autopsy* was performed 3 hours after death. The external appearance was as already described in the clinical history. The body weighed 9125 gm. and measured 98 cm. in length. The circumferences of the head, chest and abdomen were 50, 48 and 41 cm. The biparietal diameter of the head was 17 cm., and the occiput-frontal diameter 18 cm. The anterior fontanelle, which was open, measured 1.8 cm. in length and 3.2 cm. in width. The posterior fontanelle was closed. The anteroposterior diameter of the chest was 12 cm., and the transverse diameter 17 cm. The length from the suprasternal notch to the symphysis pubis was 32.5 cm. The typical facies was apparent. Hair was totally absent except for a few fine strands over the occipital region. The scalp was taut and thin, with prominent veins and negligible subcutaneous tissue. Anteriorly, over the inferior portion of the thorax and over the abdomen, the skin had a mottled, light-brown and white appearance, with a somewhat doughy consistence. In the region of the umbilicus subcutaneous fat measured 0.4 cm., but in other areas of the abdomen and throughout the body there was minimal adipose tissue. The muscles of the extremities were markedly atrophied. The joints of all the extremities bulged, and there were suggestive Heberden nodes of the fingers.

The right pleural cavity contained 20 cc. of serous fluid, and there was 30 cc. of similar fluid on the left. The pericardial cavity contained 15 cc. of serous fluid.

The heart, which weighed 110 gm., extended 5.5 cm. to the left of the midsternal line in the 5th interspace and 4.5 cm. to the right of the midsternal line in the 4th interspace. A small amount of fat was found in the atrioventricular groove and along the coronary vessels. The left ventricle measured 0.8 cm. and the right 0.3 cm. in thickness. The interventricular septum was the site of an extensive infarct, which extended into the anterior wall of the left ventricle. The infarct appeared as white fibrous tissue with a few dark hemorrhagic areas. The fibrous tissue was most marked for a distance of 0.1 to 0.2 cm. just below the endocardium and it extended from the base of the septum to the apex and from the base of the anterior wall of the left ventricle for a distance of 4.5 cm. distally to within several centimeters of the apex. On microscopical examination the infarct seemed to be at least 1 month old, with older-appearing areas as well. There was extensive replacement of muscle fibers by fibrous tissue in which there were a few scattered islands of necrotic muscle and numerous scattered blood vessels involving mainly the inner half of the myocardium. The hemorrhagic areas noted grossly proved to be proliferating blood vessels filled with blood. There was little inflammatory reaction, and no polymorphonuclear leukocytes were observed. Fragments of fresh mural thrombi were seen clinging to the endocardium of the left ventricle. Numerous sections taken from other areas of the heart showed no abnormalities. The circumferences of the valve rings were as follows: mitral, 5 cm., aortic, 3.7 cm., tricuspid, 3 cm., and pulmonary, 3.5 cm. On the inferior surface of the base of the anterior mitral cusp there was a group of yellow calcified atheromas each measuring 1 to 2 mm. in diameter. Otherwise, the valve cusps and the chordae tendineae were smooth and delicate.

*M. G. H. 15339.

The coronary ostia had pin-point diameters, and the coronary arteries revealed a severe degree of atherosclerosis, with lumens measuring a maximum of 1 to 1.5 mm. in cross-sectional diameter. The left anterior descending branch was most severely involved; at its origin, for a distance of 3 mm., the lumen appeared completely occluded by white atheromatous tissue. The distal portions of the coronary arteries at the apex were soft and patent. Microscopical study of the coronary arteries disclosed severe hyaline intimal thickening with some fat droplets and calcification. The lumen of the left anterior descending branch measured less than 1 high-power field in area in a section taken through its proximal portion, which had appeared occluded on gross inspection.

The aorta was markedly atherosclerotic, with numerous yellow intimal plaques in the descending thoracic and abdominal portions. The abdominal aorta was quite stiff whereas the remainder of the aorta had retained a moderate amount of elasticity. At the origin of the aorta just beyond the right posterior aortic cusp there were shiny, white sclerotic plaques over an area measuring 1 cm. by 1.5 cm. Exploration of the right axillary artery, which had a lumen measuring 2 to 2.5 mm. in diameter, revealed the presence of a yellow, calcified plaque narrowing the lumen to a diameter of 1 mm. for a distance of 4 mm. The remainder of the great vessels of the neck were soft and widely patent, as were the splenic, renal, iliac and right femoral arteries. Microscopical examination of the aorta showed marked hyaline intimal thickening with calcification. Similar changes were seen in a section through the plaque in the right axillary artery.

The lungs weighed 245 gm. The right middle lobe was relatively normal. The other lobes were noncrepitant and filled with edema fluid. In addition there was congestion of the lower lobes. Scattered pigment-laden macrophages and intra-alveolar hemorrhage in some areas were also noted on histological study.

The endocrine glands did not appear unusual except for the hypophysis. The thyroid gland weighed 3.5 gm. There was slight scalloping of the colloid about the periphery of the thyroid follicles; the epithelium was cuboidal. There was no evidence of hyperactivity.

The 2 lower parathyroid glands were identified; they had a normal, yellow-brown appearance, and each measured 0.4 cm. by 0.2 cm. by 0.2 cm. There was a minimal amount of fat, and no oxyphil cells were present.

There was 5.7 gm. of soft, pinkish-gray thymic tissue, which consisted of lymphocytes and scattered Hassall corpuscles. No medullary germinal centers were seen. There were occasional foci of fat on microscopical examination.

The adrenal glands weighed 3.2 gm. together. Their architecture was normal in a hematoxylin and eosin section. Histochemical studies, including the Schiff, Ashbel-Seligman, Windaus and Schultz reactions, as well as a Sudan IV stain, failed to reveal any abnormalities.

The right testis weighed 1.7 gm., and the left 2 gm. Both showed a prepubertal structure, without spermatogenesis. Leydig cells were not identified. The penis was normal in size.

The pancreas and prostate, which were not remarkable, weighed 23 and 1.7 gm.

Differential cell counts were done on 3 widely spaced sections of the anterior hypophysis stained by the periodic acid-Schiff technic with an orange-G counterstain,* and the following cell types were differentiated: normal basophils, hyaline basophils, amphophils (sparsely granulated basophils of Mellgren[10]), hypertrophic amphophils, acidophils and chromophobes. The differential count in this patient was compared in the following table with the counts of 3 other children of normal weight, height and general development by the same technic (Table 1); it is realized that these were not strictly "normal" children since their hypophyses had been subjected to the stress of a severe terminal illness. A slight decrease in the number of acidophils was found in comparison with the controls.

The calvarium measured 2 mm. in thickness; it was firm and solid without any distinction between inner and outer tables. At the level of the 4th rib the distance from the midsternal line to the costochondral junction was 5 cm. The right hip joint was opened, and no abnormalities were encountered. The acetabulum and the femoral head had smooth, white, glistening surfaces. The upper third of the right femur was removed, and on cut section it was noted that the cortex averaged 2 to 3 mm. in thickness. Proximal to the epiphyseal line the marrow of the femoral head was yellow, whereas distally in the shaft it was light red and mushy. The marrow of the femoral head and neck was firm, with many hard bone spicules. The rib marrow contained many coarse bone spicules, and not much marrow could be squeezed out of the ribs. The vertebral marrow did not appear unusual. Miscroscopical study of the femur and ribs demonstrated slight chondromatous transformation into bone. Considerable hematopoesis was seen in the femoral marrow from the upper third of the femur. The marrow of the vertebras and ribs was normal.

TABLE 1. *Differential Cell Counts on Adenohypophysis.**

Autopsy No.	Sex	Age yr.	Diagnosis	Weight of Hypophysis gm.	Cells Counted per cu. mm.	Normal Basophils %	Amphophils %	Acidophils %	Chromophobes %	Hypertrophic Amphophils %	Hyaline Basophils %
15339	M	11 3/12	Progeria; myocardial infarct.	0.33	3628	9.4	12.7	18.8	54.2	4.0	0.9
16334	M	9 4/12	Poliomyelitis; pneumonia.	0.29	4374	5.7	19.1	25.2	49.2	0.8	—
16348	M	9	Acute rheumatic fever	0.29	4915	9.6	18.0	25.3	45.4	1.7	—
16462	F	6 9/12	Head injury (craniotomy)	0.28	4775	12.2	10.8	25.1	50.4	1.5	—

*Periodic acid-Schiff technic, with orange-G counterstain.

The brain weighed 1300 gm. The pia arachnoid overlying the dorsolateral and basal surfaces was somewhat thickened. The cerebral arteries at the base of the brain showed no sclerosis. The superficial blood vessels over the dorsolateral surfaces of the brain were moderately congested. Over the medial surface of the left frontal lobe, 3 cm. from the anterior pole, there was a soft, depressed area measuring 2.5 by 1.5 cm. This area included the superior frontal gyrus and part of the cingulate gyrus, but it did not extend posteriorly as far as the paracentral lobule. The brain was sectioned after fixation. Cut section disclosed severe congestion of the vessels throughout the brain. In the left frontal lobe, where the lesion had been noted externally, there was destruction of the cortex and underlying white matter, with cavitation and yellowish discoloration. Microscopical examination of this lesion revealed a well developed glial reaction indicative of a quiescent process. In another section from the left frontal lobe there was a small focus of incomplete necrosis characterized by disappearance of nerve cells and a reactive glial response. With these exceptions the sections of the brain, including the brain stem and cerebellum, were within normal limits. Except for more proliferation of ependymal cells of the central canal than would be expected in a child of this age, the spinal cord demonstrated no abnormalities. The neurohypophysis was normal. The pineal body was not examined.

The kidneys, which weighed 118.3 gm. together, were

unremarkable. On microscopical study the renal arteries and arterioles appeared free of disease. The ureters, urinary bladder and seminal vesicles did not show any abnormalities.

Skin from the abdomen disclosed an increase in hyaline in the lower portion of the dermis. The elastic fibers appeared normal in the upper dermis. Several foci of lymphocytes were noted within the hyaline tissue. There was a slight amount of subcutaneous fat. A section of skin from the leg was normal. Sections of skeletal muscle revealed no abnormalities.

The gastrointestinal tract was normal. Mesenteric fat was minimal. The mesenteric and retroperitoneal lymph nodes were not unusual. The spleen weighed 28 gm. and was normal.

Discussion

This case is almost identical to the one reported by Talbot et al.[11] from this hospital. As in that case it was concluded by those following the patient clinically that this patient suffered from a disturbance characterized by excessive energy metabolism with few calories available for growth. The hypermetabolism could not be explained by any thyroid abnormality at autopsy. The high creatinine coefficient denotes the relatively high proportion of muscle mass in the body. Cooke[7] believes that the apparently increased metabolic rate in this disease is an indication of a greater proportion of active metabolic tissue than in a normal child, in whom a considerable amount of inactive adipose tissue is present. Talbot,[12] however, points out that these children have a high proportion of muscle because they have metabolized everything else. Another point of interest was the presence of scleroderma, which has previously been described in progeria.[13-15] The immediate cause of death was congestive heart failure resulting from severe coronary-artery disease and myocardial infarction. The cause of the hypertension remains obscure. No cause for the cerebral bruit was found at autopsy.

Thomson and Forfar[5] consider the underlying lesion in progeria to be a dysfunction of the eosinophil cells of the anterior pituitary gland. They cite the following evidence: points of similarity between progeria and Simmonds's disease, abnormalities of the sella turcica noted on x-ray study, a cyst in the pars intermedia with increased size and fine granularity of the eosinophil cells in the case reported by Orrico and Strada,[16] asymmetry of the pituitary in the case of Talbot et al.[11] and a decreased number of eosinophil cells in Manschot's[17] case. They also conclude that since hyperfunction of the eosinophils may produce the changes of acromegaly, hypofunction of these cells may result in the changes of progeria. In the case reported above there was a slight decrease in the eosinophils as compared with both the controls and the normal range established by Rasmussen[18] in glands studied with the Mallory trichrome technic. Manschot's[17] figure of 16.3 per cent eosinophils in a twenty-seven-year-old patient with progeria also represents a slight decrease. However, these pituitary changes are similar to those seen in many other diseases, and a slight decrease in eosinophils does not seem sufficient evidence for the hypophyseal origin of progeria. In the dwarf mice studied by Smith and MacDowell[19] no acidophils were said to be present. In a seventy-six-year-old ateliotic female dwarf described by Hewer[20] acidophils made up only 0.2 per cent of the total cell count. Because the correlation between structure and function in the hypophysis is as yet imperfectly understood one cannot draw any final conclusions on the basis of the data mentioned above. The presence of appreciable numbers of hyaline basophils and the high percentage of hypertrophic amphophils suggest a high level of hypophyseal-adrenal activity,[10] but whether this is secondary to heart failure and shock cannot be definitely concluded.

The anatomic findings in this case fail to elucidate the part, if any, that the other endocrine glands might play in the etiology of this condition. They lend no support to the theories of a pluriglandular process suggested by Nasso[21] and Orrico and Strada[16] or of an adrenal origin of the disease as proposed by Variot and Pironneau.[22] Kölbl et al.,[23] in describing 2 cases similar to progeria, suggest that this disease be considered a congenital defect since there are cases similar to progeria but with microphthalmia, cataract and cerebral calcification. Wiedemann[24] regards progeria as a constitutional mesenchymal dysplasia. Manschot[17] states that the disease is a particular form of pituitary dwarfism combined with inadequate development of tissue derived from the mesenchyme. Talbot and his associates[11] believe that these children suffer from an inborn error of metabolism involving an enzyme of importance in the energy-metabolism cycle. More information must be accumulated before any definite conclusions can be drawn concerning the etiology of this disease.

Summary

A case of progeria (Hutchinson–Gilford syndrome), believed to be the twenty-third in the literature, is described with autopsy findings. This child survived to the age of eleven years and three months, when death resulted from severe coronary-artery disease with myocardial infarction.

In this case, as well as in another previously autopsied, there was a slight decrease in the number of eosinophil cells of the anterior lobe of the hypophysis. The significance of this is not fully understood. The etiology of the disease is as yet unknown.

I am indebted to Dr. Agnes S. Burt, who studied the pituitary gland in this case, and to Dr. Nathan B. Talbot for his helpful criticism.

References

1. Hutchinson, J. Congenital absence of hair and mammary glands. *Tr. Med.-Chir. Soc. Edinburgh* **69**:473-477, 1886.
2. Gilford, H. On condition of mixed premature and immature development. *Tr. Med.-Chir. Soc. Edinburgh* **80**:17-45, 1897.
3. Manschot, W. A. Een Geval van Progero-nanie (Progeria van Gilford). *Nederl. tijdschr. v. geneesk.* **84**:3774-3782, 1940.
4. *Idem.* Case of progeronanism (progeria of Gilford). *Acta paediat.* **39**:158-164, 1950.
5. Thomson, J., and Forfar, J. O. Progeria (Hutchinson-Gilford syndrome). *Arch. Dis. Child.* **25**:224-234, 1950.
6. Rossi, E. Uber einem neuen Fall von Progeria (Hutchinson-Gilford Syndrom). *Helvet. paediat. acta* **6**:165-171, 1951.
7. Cooke, J. V. Rate of growth in progeria with report of 2 cases. *J. Pediat.* **42**:26-37, 1953.

8. Doub, H. P. Progeria. *M. Radiog. & Photog.* **29**:60-62, 1953.
9. Pearse, A. G. E. Cytochemistry and cytology of normal anterior hypophysis investigated by trichrome-periodic acid-Schiff method. *J. Path. & Bact.* **64**:811-826, 1952.
10. Mellgren, J. Anterior pituitary in hyperfunction of adrenal cortex: anatomical study with special reference to syndroma Morgagni and notes on prostatic hypertrophy. *Acta path. et microbiol. Scandinav. Supp.* **60**:1-177, 1945.
11. Talbot, N., et al. Progeria: clinical, metabolic and pathologic studies on patient. *Am. J. Dis. Child.* **69**:267-279, 1945.
12. Talbot, N. Personal communication.
13. Strunz, F. Ein Fall von Progeria, beginnend mit ausgedehnter Sklerodermie. *Ztschr. f. Kinderh.* **47**:401-416, 1929.
14. Zeder, E. Über Progerie, eine seltene Form des Hypophysären Zwergwuchses mit diffuser Sklerodermie. *Monatschr. f. Kinderh.* **81**:167-205, 1940.
15. Exchaquet, L. un cas de progéria. *Rev. franç. de pédiat.* **11**:467-481, 1935.
16. Orrico, J., and Strada, F. Étude anatomo-clinique sur un cas de nanisme sénile (progérie). *Arch. de méd. d. enf.* **30**:385-398, 1927.
17. Manschot, W. A. De Getaalverhouding der Celsoorten in de Hypophysevoorkwab van den Mensch. *Nederl. tijdschr. v. geneesk.* **84**: 3782-3787, 1940.
18. Rasmussen, A. T. Changes in proportion of cell types in anterior lobe of human hypophysis during first nineteen years of life. *Am. J. Anat.* **86**:75-89, 1950.
19. Smith, P. E., and MacDowell, E. C. Hereditary anterior pituitary deficiency in mouse. *Anat. Rec.* **46**:249-257, 1930.
20. Hewer, T. F. Ateleiotic dwarfism with normal sexual function: result of hypopituitarism. *J. Endocrinol.* **3**:397-400, 1944.
21. Nasso, I. Progeria. *Pediatria* **33**:1213-1224, 1925.
22. Variot and Pironneau. Nanisme avec dystrophie osseuse et cutanée spéciales: soupçon d'agénésie des capsules surrénales. *Bull. Soc. pédiat. de Paris* **12**:307-314, 1910.
23. Kölbl, H., Zierhut, H., and Zweymuller, E. Beitrag zur Pathogenese der Progerie an Hand von zwei neuen Fällen. *Österr. Ztschr. f. Kinderh.* **8**:162-178, 1952.
24. Wiedemann, H. R. Über Greisenhaftigkeit im Kindesalter, insbesondere die Gilfordsche Progerie: zugleich ein Beitrag zum Bereich der mesodermalen Dysplasien. *Ztschr. f. Kinderh.* **65**:670-697, 1948.

USE OF CORTISONE DURING PENICILLIN TREATMENT OF SECONDARY MUCOCUTANEOUS SYPHILIS IN A HYPERSENSITIVE PATIENT

MARVIN BRODEY, M.D.,* AND CARL T. NELSON, M.D.†

NEW YORK CITY

PREVIOUS studies[1,2] have shown that the administration of cortisone to rabbits with untreated experimental syphilis suppresses the usual response of the host to the treponemes and permits the unrestrained proliferation of the micro-organisms in the lesions and blood stream. Apparently, the ability of cortisone to promote the spread of untreated syphilitic infection is comparable to that encountered after the administration of ACTH and cortisone in tuberculous and pneumococcal infections.[3-8] Although reports on the effect of ACTH and cortisone in the late stages of human syphilis are available[9,10] there is little information regarding the use of corticosteroids in the early infectious stages of this disease in man. Robinson[11] administered cortisone to 3 patients with dark-field-positive primary lesions and found that the lesions became dry and dark-field negative within forty-eight hours. With the cessation of therapy a rebound phenomenon was noted, resulting in moist and larger lesions. These patients were then treated successfully with penicillin.

In the case reported below a patient with secondary (late recurrent) mucocutaneous syphilis was treated simultaneously with cortisone and penicillin. He was unusually hypersensitive to penicillin, responding to small doses of the antibiotic with a severe serum-sickness type of reaction. Cortisone was used to control the urticaria and angioedema induced by penicillin during the course of antisyphilitic therapy. We believe that the need for intensive treatment, as evidenced by mucocutaneous relapse and the persistence of positive spinal-fluid findings, as well as the recurrent episodes of severe angioedema despite large doses of antihistaminic drugs, justified this maneuver. The use of cortisone in the presence of active syphilitic infection appears to be a safe procedure if the hormone is adequately covered by effective penicillin therapy.

*Assistant dermatologist, Vanderbilt Clinic, Presbyterian Hospital.

†Professor of dermatology, Columbia University College of Physicians and Surgeons; director of dermatology, Presbyterian Hospital.

CASE REPORT

T.M., a 30-year-old man, was admitted to the hospital on February 14, 1951, because of intense pruritus of the scalp; severe generalized urticaria; swelling and redness of the throat; edema of the head, neck, feet and hands; swollen, painful joints and a temperature of 102°F. Three years previously he had received an injection of penicillin for a "3-day-old chancre." On the following day an eruption developed that responded to ephedrine and antihistamines. During the following year he allegedly received bismuth, arsenicals and 6,000,000 units of penicillin, after which the serologic tests for syphilis were reported negative. One year later the tests in the blood and spinal fluid were positive. Because an intradermal test in the right forearm with crystalline sodium penicillin G at that time was positive the patient was treated with arsenicals for 5 months. In February, 1951, he received a single injection of 600,000 units of crystalline procaine penicillin G in aqueous suspension. Within 24 hours redness and itching were noted at the site of the previous intradermal test with penicillin. On admission the diagnosis was urticaria and angioedema due to hypersensitivity to penicillin.

After treatment with epinephrine, ephedrine, acetylsalicylic acid and diphenhydramine hydrochloride the serum-sickness type of reaction subsided, and the patient was discharged in 10 days. Transient urticaria, however, persisted for another month. In April, because of the persistently positive reaction in the blood and spinal fluid, penicillin therapy was again attempted. The penicillin salt of 1,2-diphenyl-2-hydroxyethylamine, 50,000 units intramuscularly every 3d day, was started, but 5 hours after the 3d injection generalized urticaria recurred and bullae developed on the right forearm at the site of the previous intradermal injection of penicillin. The fever, generalized urticaria and arthralgia became more severe, and the patient was readmitted to the hospital. He received 75 mg. of ACTH and 300 mg. of cortisone during the 1st 24 hours, 300 mg. of cortisone daily for the next 3 days and 100 mg. on the 5th day. Symptoms subsided within 48 hours of the initial dose of corticosteroids, and the skin was clear except for residual erythema and edema of the forearms and crusting at the sites of the bullae. Because of the strongly positive Wassermann reactions in the blood and spinal fluid, the patient was given chlortetracycline, 3 gm. daily for 7 days and then

2 gm. daily for the next 27 days, for a total of 75 gm.

He appeared well for approximately 1 year after the completion of treatment with chlortetracycline. The serologic tests in the blood remained positive but at a fixed low titer (VDRL*=1:2). In September, 1952, he returned to the clinic because of redness and soreness of the throat, enlarged cervical lymph nodes and a scaly, erythematous, slightly pruritic papular eruption on the penis and the flexor surfaces of the hands and wrists. Dark-field examinations of the cutaneous lesions on three successive days showed no *Treponema pallidum,* but a biopsy of a scaly papule 2 days later yielded dark-field-positive material. The titer of the VDRL test in the blood had risen to 1:16 (subsequently to 1:32). The patient was advised to begin arsenical and bismuth therapy again. Because conditions of his employment did not permit regular attendance at this clinic arrangements were made to administer treatment at a clinic of the New York City Department of Health. After 2 injections of bismuth the cutaneous lesions allegedly disappeared, and he permitted treatment to lapse. He was lost to follow-up study for approximately 2 months. In November, he reappeared because of a cutaneous eruption similar to that seen 2 months previously. Owing to his lack of co-operation and his inability to attend the clinic regularly, he was admitted to the hospital for intensive therapy with penicillin. It was planned to prepare him with heavy doses of diphenhydramine hydrochloride and if necessary, to use cortisone to control the manifestations of hypersensitiveness to penicillin.

On admission he was given diphenhydramine, 100 mg. every 3 hours. After 36 hours crystalline penicillin G in aqueous solution, 50,000 units intramuscularly every 3 hours, was started. Twenty-four hours after the 1st injection there was massive urticaria of the trunk and legs, with redness and swelling of the arms. During the next 24 hours he received 200 mg. of cortisone in divided doses and then was maintained on a daily dosage of 100 mg. Within 48 hours of the initial dose the erythema, wheals and edema decreased greatly, and he was subjectively improved. During this time the injections of crystalline penicillin, 50,000 units each, were continued every 3 hours. On the 4th day of therapy the penicillin dosage was increased to 150,000 units every 3 hours. This was continued for 3 weeks until a total of 28,000,000 units had been given. Cortisone, 100 mg. daily, and diphenhydramine, 700 mg. daily, were continued for 18 days. On the 5th day after starting cortisone the patient was entirely asymptomatic and remained so throughout the remainder of treatment. Four days before the completion of penicillin therapy reduction of the dosage of cortisone by decrements of 12.5 mg. daily was begun, and the daily dosage of diphenhydramine was lowered to 400 mg. Four days after discharge from the hospital cortisone was stopped, but diphenhydramine was continued at a level of 400 mg. daily. One week later, when the diphenhydramine was discontinued, a few small urticarial wheals were noted. These disappeared on the reinstitution of diphenhydramine. Within a month no further antihistamines were required, and during the past 14 months the patient has remained asymptomatic, the blood and spinal fluid continuing to show a decline in serologic activity (Fig. 1).

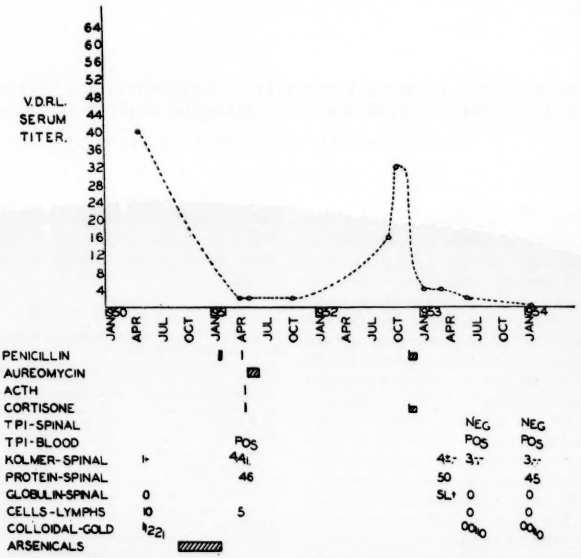


FIGURE 1. *Serologic and Cerebrospinal-Fluid Response in a Patient with Recurrent Secondary Syphilis Treated with Cortisone and Penicillin.*

*Flocculation test for syphilis devised by the Venereal Disease Research Laboratory of the United States Public Health Service.

DISCUSSION

It is possible that this patient had a dissemination of *T. pallidum* during the five days of corticosteroid therapy for the episode of urticaria and angioedema in 1951. This, together with an inadequate response to chlortetracycline, may have been an important factor in the mucocutaneous relapse a year later. As shown in Figure 1, the serologic titer fell appreciably during the combined cortisone and penicillin therapy.

Although this may be interpreted as a diminished ability to produce syphilitic reagin during the administration of cortisone it should be noted that there was no rebound of reagin titer after the cessation of cortisone therapy. Nor was any effect on the treponemal immobilization test observed after cortisone treatment, contrary to the suggestion of Durel and his associates.[12]

Summary

A case of infectious secondary (late recurrent) syphilis treated simultaneously with cortisone and penicillin is presented. Cortisone was given to control the severe symptoms of hypersensitiveness to the antibiotic.

It appears that cortisone may be employed safely in situations of this sort if large doses of penicillin are given at the same time to control the syphilitic infection.

References

1. Turner, T. R., and Hollander, D. H. Cortisone in experimental syphilis. *Bull. Johns Hopkins Hosp.* **87**:505-509, 1950.
2. DeLamater, E. D., Saurino, V. R., and Urbach, F. Studies on immunology of spirochetoses: effect of cortisone on experimental spirochetosis. *Am. J. Syph.* **36**:127-139, 1952.
3. Bing, M. Growth-inhibiting properties of steroids. *Brit. M. J.* **1**:846, 1950.
4. Hart, P. D'A., and Rees, R. J. W. Enhancing effect of cortisone on tuberculosis in mouse. *Lancet* **2**:391-395, 1950.
5. Michael, M., Jr., Cummings, M. M., and Bloom, W. L. Course of experimental tuberculosis in albino rats as influenced by cortisone. *Proc. Soc. Exper. Biol. & Med.* **75**:613-616, 1950.
6. Spain, D. M., and Molomut, N. Effects of cortisone on development of tuberculous lesions in guinea pigs and on their modification by streptomycin therapy. *Am. Rev. Tuberc.* **62**:337-344, 1950.
7. Lurie, M. B., Zappasodi, P., Dannenberg, A. M., and Swartz, I. B. Effect of cortisone on pathogenesis of tuberculosis. *Science* **113**: 234-237, 1951.
8. Kass, E. H., Ingbar, S. H., and Finland, M. Effects of adrenocorticotropic hormone in pneumonia: clinical, bacteriological and serological studies. *Ann. Int. Med.* **33**:1081-1098, 1950.
9. Ashworth, A. N. Cortisone in treatment of syphilitic eye disease. *Brit. J. Ven. Dis.* **29**:3-11, 1953.
10. Kass, E. H., Ingbar, S. H., Lundgren, M. M., and Finland, M. ACTH in malaria induced in syphilitics. *New Eng. J. Med.* **245**: 1000-1002, 1951.
11. Robinson, R. C. V. Newer antibiotics in treatment of venereal disease. *Brit. J. Ven. Dis.* **28**:80-88, 1552.
12. Durel, P., Saussé, A., and Borel, L. J. Treponema immobilization test: results of 1,000 observations. *Brit. J. Ven. Dis.* **28**:68-79, 1952.

MEDICAL PROGRESS

ANESTHESIOLOGY (Concluded)*

E. M. Papper, M.D.,† and S. H. Ngai, M.D.‡

NEW YORK CITY

Infant Resuscitation

The provision of a painless labor for the mother is always accompanied by the possibility of respiratory depression of the newborn infant by anesthetic agents. Obstetric complications in addition to prematurity and malformation of the newborn can interfere with normal respiratory and circulatory functions, and are responsible for many neonatal complications and deaths. The value of most methods of infant resuscitation has not been on a secure basis since gross survival rates have been the only clinical measure of success or failure. To establish objectively the condition of the newborn Apgar[142] proposed a new method of clinical evaluation. Sixty seconds after delivery has been completed 5 objective signs are evaluated, each giving a score of 0, 1 or 2. A heart rate of over 100 per minute is given a score of 2, one below 100 is graded 1, and one that is absent is classified 0. Similar scores are given for respiratory efforts, muscle tone, response to catheter stimulation in the nostril and color. A total score of 10 indicates an infant in the best possible condition, and a score of 0, a dead infant. This method of evaluation is simple and can be accomplished in a short time without interfering with immediate neonatal care. Apgar has applied the method with success in the evaluation of over 2000 infants and correlated the results with anesthetic and obstetric management.

Adequate oxygenation of the newborn is considered essential not only for survival but also for the normal development of mentality. Apgar and her co-workers[143] have attempted to correlate the adequacy of oxygenation of infants shortly after birth with their intelligence in later years of life. In over 200 infants the heel-blood oxygen saturation (capillary blood) was determined shortly after birth. At the age of five intelligence quotients were evaluated with a series of intelligence tests. There did not appear to be any correlation between anoxia at birth and subsequent intelligence at the age of five as measured in this fashion. Although factors other than neonatal oxygenation determine the subsequent development of mental functions, this study suggests that nonfatal anoxia does not result in cerebral damage that could be demonstrated with standard intelligence tests. However, regardless of this and other considerations, it should be emphasized that infant resuscitation is of paramount importance to prevent death from asphyxia.

The standard resuscitative measures for the apneic newborn infant may require modification. Recent investigations of Day et al.[144] indicated that the usual

*From the Anesthesiology Service, Presbyterian Hospital, and the Department of Anesthesiology, Columbia University College of Physicians and Surgeons.

†Professor of anesthesiology, Columbia University College of Physicians and Surgeons; director, Anesthesiology Service, Presbyterian Hospital.

‡Associate in anesthesiology, Columbia University College of Physicians and Surgeons; assistant anesthesiologist, Presbyterian Hospital.

positive pressures of less than 20 mm. of mercury may be totally inadequate to effect expansion of an atelectatic infant lung. From their study it seems that relatively high pressures were necessary and could be safely applied if the duration of the positive pressure phase is a fraction of a second. Further critical evaluation of this method of resuscitation is indicated before extensive clinical trial is warranted.

Other means of resuscitation have been proposed and evaluated. Bloxsom[145] constructed a pressure chamber for infant resuscitation, the Bloxsom air lock. With the entire infant placed in the chamber the pressure was varied from 50 to 150 mm. of mercury alternatively. He stated that it can effect better removal of fluid from the infant's lung, better absorption of oxygen through the skin and more efficient aeration of atelectatic lungs. Apgar and Kreiselman[146] conducted studies in apneic dogs to evaluate the efficacy of this device. They found that apneic animals were asphyxiated quite promptly after being placed in this chamber. Furthermore, there was no evidence to support the contention that intrabronchial movement of fluid or other matter occurred. The suggested advantages of the Bloxsom air lock were not substantiated in this study.

Anesthetic Barbiturates

Since thiopental was introduced in 1935 as an anesthetic agent for intravenous use it has gained wide clinical acceptance for its fast and pleasant action. However, the belief that the drug was a short-acting barbiturate was not substantiated since prolonged depression and somnolence often followed a moderate or large dose. Brodie and his co-workers[147] developed a precise analytical technic for accurate and specific measurement of thiopental concentrations in plasma and tissues that was used to study the physiologic disposition of the drug in the body. Brodie et al.[147-149] found that the plasma decay curve showed two distinctive phases after the intravenous injection of thiopental. The first phase represented the period of tissue localization, and the second the period of drug degradation. As the thiopental concentration in the plasma decreased, the concentration in fat gradually increased.[150] At the end of three or four hours the thiopental concentration in the fat was four or five times that of the plasma. Thus, it was concluded that the initial drop of the plasma concentration was due to the redistribution of the drug in the body from the water phase into tissues, especially fat.[147-150] After equilibrium was established the rate of degradation was determined to be 10 to 15 per cent per hour.[147]

The preferred site of localization of thiopental in the body fat was confirmed by Bollman and his associates,[151] using S^{35} thiopental in laboratory animals, and also by Shideman and his co-workers[152] in man and in animals. The latter group showed that equilibrium is attained in one and one-half to two and one-half hours after injection of thiopental in man; in dogs it required four hours for the fat concentration to reach the maximum.

Nearly all the injected thiopental is detoxified in the body. Brodie et al.[147] could recover only 0.3 per cent of the administered dose from the urine for the twenty-four-hour period after injection. They isolated from the urine one of the metabolites, thiopental carboxylic acid, the oxidative product of thiopental. However, thiopental carboxylic acid accounted for only 10 to 25 per cent of the administered dose. Taylor, Richards and Tabern,[153] using S^{35} thiopental to trace the fate of the drug in laboratory animals, found that 86.2 per cent of the total radioactive sulfur could be recovered from the urine, of which 14 per cent was chloroform extractable (including thiopental carboxylic acid) and 17 per cent inorganic sulfate. Paper chromatography indicated that at least 12 radioactive compounds were present. These workers suggested three possible modes of destruction of thiopental: oxidation of the side chain; enzymatic removal of the sulfur; and splitting up of the malonylurea ring.[154] However, no direct evidence was given for the third possibility.

The site of destruction of thiopental was the subject of much controversy. Earlier workers[155-158] showed in animal experiments that the narcotic action of thiopental was not prolonged after the liver had been damaged with chloroform or carbon tetrachloride, or after a 70 per cent hepatectomy. They concluded that the liver was not the major site of detoxication. Clinically, it was also the impression of Lundy and Adams[159] that the presence of liver disease does not contraindicate the use of thiopental. However, Dorfman and Goldbaum[160] demonstrated that liver slices can detoxify thiopental in vitro. Shideman et al.[161-164] reported that the sleeping time after injection of thiopental was greatly prolonged (750 to 1169 per cent) if the liver was damaged with chemicals or blood diverted from the liver with an Eck fistula or after a 90 per cent hepatectomy. Furthermore, they followed the decay curves of thiopental in plasma in perfusion experiments.[163] With heart-lung preparations the decline of plasma concentration of thiopental was very slow. The inclusion of kidney changed the rate of decline to some extent, but the inclusion of liver greatly hastened the rate of degradation. They also compared the duration of thiopental narcosis in patients who had normal hepatic function with patients whose livers were damaged (bromsulfalein retention up to 40 per cent). The duration of narcosis in the latter group was three times as long as that in the group with normal liver function.[165] It appears reasonable to conclude that the liver is an important site of detoxication of thiopental.

The role of the kidney in the detoxication of thiopental is not clearly defined at present. Dorfman and Goldbaum[160] reported degradation of thiopental by kidney slices in vitro. Shideman and Kelly[163,164] showed, in heart-lung preparations, that the inclusion of the kidney hastened the decline of plasma concen-

tration of thiopental to some extent. Richards and his co-workers[166] observed, within an hour of bilateral nephrectomy, that the sleeping time from thiopental was not prolonged, but from then on, the sleeping time became progressively prolonged. This prolongation was correlated directly with the rise in blood nonprotein nitrogen concentration. The absence of the kidney and the presence of an accumulation of nitrogenous substances greatly retarded the rate of degradation. It seems likely that although thiopental may be destroyed in the kidney, this organ is not as important as the liver.

Two other short-acting barbiturates were introduced for use in clinical anesthesia—Surital and Kemithal. Surital is the sulfur analogue of secobarbital, and Kemithal is a thiobarbiturate with a cyclic radical at the 5 position, (5-Δ2, 3-cyclo-hexeny 1-5 alkyl - 2-thiobarbiturate). According to various clinical reports[167-173] their action and the duration of narcosis are not significantly different from those of thiopental. Brodie et al.[149,174] studied their fate in man and found that they are also localized in the body fat after administration, and the rate of degradation is not materially different from that of thiopental.

Swanson and Chen[175] synthesized a series of N-substituted thiobarbiturates in a search for a true short-acting barbiturate and found that two of the N-methylated compounds showed less cumulative action than thiopental in laboratory animals. Peterson and his associates[176] studied the fate of N-methyl thiopental and the N-methyl derivative of Surital in dogs and in man. Although these two compounds have a higher affinity for the body fat, which explains their shorter action, the rate of degradation is still slow—about 10 per cent per hour.

Because of the slow rate of degradation of the presently available short-acting barbiturates, they should be used only as a supplement to other anesthetic agents. Large doses should be avoided to prevent prolonged postanesthetic depression. There is need for a new intravenously administered agent that can be detoxified in the body at a rapid rate.[149,177]

Anesthesia during Induced Hypotension

The establishment of a bloodless field facilitates many surgical procedures and sometimes, when the lesion is highly vascular, determines the outcome of the operation. To provide a bloodless field Gardner[178] used controlled hemorrhage with arteriotomy, reducing the arterial blood pressure to a hypotensive level. He claimed that operation was made easier and that the blood loss from the operative site decreased. Griffiths and Gillies,[179] using high spinal anesthesia with postural adjustment to lower the arterial pressure, also obtained a "dry" field for surgery. They reasoned that, if the arterioles were widely dilated with spinal block, the effective perfusing pressure in the capillaries would remain the same as that before the induction of hypotension. If this assumption is correct, the blood flow through the organs and their oxygenation should not be altered significantly.

In 1949 Paton and Zaimis[180] studied the actions of a series of bis-quaternary ammonium compounds with polymethylene chains and found that pentomethonium and hexamethonium compounds have a powerful ganglionic blocking action. Since then pentamethonium and hexamethonium have been used in clinical anesthesia to induce hypotension for the purpose of providing a bloodless field. During anesthesia the drug is given intravenously, and the patient's position is adjusted to induce postural hypotension. Despite the fact that few quantitative studies were carried out to determine the effect of induced hypotension on hemodynamics and vital organs early clinical reports were enthusiastic about the advantages of this technic. As time passed and more hypotensive anesthesias were done the dangers and shortcomings of "physiologic trespassing" became evident and recognized. Davison,[181] after two years of experience with hypotensive anesthesia, pointed out the dangers of the profound circulatory alterations and their disastrous side effects. Because the possibility of cerebral anoxia, renal damage, vascular thrombosis, and reactionary hemorrhage is ever present with hypotensive anesthesia, he stated that this procedure should not be adopted except in the extremely rare cases in which operation would be technically impossible without a bloodless field, which could not be more safely obtained by some other methods, and unless death or really serious disability would certainly result if the operation was not carried out.

Hampton and Little[182] reported the results of a questionnaire directed to anesthesiologists in Britain concerning hypotensive anesthesia. In the majority of cases a blood pressure lower than 80 was obtained with methonium compounds or spinal anesthesia. In a series of 21,125 cases the over-all mortality was 0.2 per cent (1:500). The major causes of death were cerebral anoxia or thrombosis, renal failure, coronary thrombosis and cardiac arrest. The incidence of complications was even higher: 1 in every 38 cases. In addition to the symptoms related to cerebral anoxia and renal damage reactionary hemorrhage and delayed recovery were commonly encountered. A similar survey among American anesthesiologists was carried out by the same authors.[183] The over-all mortality and incidence of complications from hypotensive anesthesia were comparable to those in Britain. However, an important point was learned from this survey: when the systolic pressure was kept at 80 or above few complications occurred. The authors stated that the results of these surveys should by no means lead to the conclusion that hypotensive anesthesia should be barred from clinical practice. Definite indications should exist, and any contraindication should be respected. Among the more important contraindications cited were cardiovascular diseases, renal diseases and reduced blood volume. It was also stated that hypo-

tensive anesthesia was relatively safe if the systolic pressure was kept at or above 80.

Rakita and Sancetta[184] found that, after intravenous injection of hexamethonium to conscious normotensive subjects, the mean arterial pressure was reduced 20.3 per cent, and the total peripheral resistance decreased 17.0 per cent. The cardiac index was not significantly altered. Grob et al.[185,186] observed the effects of hexamethonium and pentamethonium on conscious hypertensive subjects. With slight reduction in arterial pressure, the stroke volume and cardiac output were increased, accompanied by a fall in the total peripheral resistance. With moderate to marked reduction in arterial pressure, the cardiac output was decreased. The total peripheral resistance was either not changed or slightly increased. The coronary blood flow showed no change or declined with a lowered coronary vascular resistance.

Shackman and his associates[187] studied the effects of methonium-induced hypotension in man during light anesthesia. When the peripheral blood flow (limb flow) was high pentamethonium reduced both the cardiac output and limb flow to approximately 60 per cent of the control, with the arterial pressure at 55 per cent of the control level. When the hypotension was induced during the period with low limb flow, the cardiac output was reduced to 47 per cent, with a comparable fall of arterial pressure, and the limb flow was not changed. Murphy and his coworkers[188] observed in normotensive dogs that the arterial pressure decreased 13 per cent, and cardiac output 31 per cent after the injection of hexamethonium. The coronary blood flow fell 15 per cent, with an increase in oxygen extraction so that the oxygen uptake of the heart was not changed. Gilmore et al.[189] found in conscious subjects that the circulation time was greatly prolonged during induced hypotension with hexamethonium. From these findings, it can be concluded that the cardiac output is increased after a slight fall of arterial pressure. However, when the hypotension is moderate or severe the cardiac output is actually decreased, presumably owing to pooling of blood in the postarteriolar bed. Although the coronary vascular resistance is reduced the coronary blood flow suffers a fall, and the oxygenation of the myocardium is maintained at the expense of a higher arteriovenous oxygen difference. It becomes obvious that hypotensive anesthesia is definitely contraindicated in patients with heart diseases, especially those with coronary arteriosclerosis and insufficiency.

The brain is another organ that cannot tolerate anoxia. A reduction in the cerebrovascular resistance can compensate for the drop in arterial pressure to a certain extent to maintain the cerebral blood flow and cerebral oxygenation.[190] If the arterial pressure falls below a critical level these compensatory mechanisms will fail, and cerebral anoxia will be inevitable. Nilsson,[191] using the flicker fusion method for testing the function of the retina, optic nerves and optical cortex, found that 6 out of 15 patients who had hypotensive anesthesia showed positive tests, indicating cerebral damage postoperatively. Ngai and Nelson[192] recorded the changes of arterial pressure and cerebral blood flow through the internal carotid arteries continuously during induced hypotension in dogs; they reported that the cerebral blood flow decreased proportionately to the fall of arterial pressure. Morris et al,[193] using the nitrous oxide method of Kety, studied the effects of controlled hypotension on cerebral circulation in 10 conscious patients in the supine position. With the arterial pressure at 61 per cent of control levels the cerebral blood flow was reduced to 70 per cent of normal. The cerebrovascular resistance was lowered to 89 per cent, and the cerebral oxygen uptake to 88 per cent of the control values. These changes were also accompanied by an increase of the arterial and internal jugular venous oxygen difference. Finnerty, Witkin and Fazekas[194] measured the cerebral blood flow in 8 conscious subjects before and during hexamethonium-induced hypotension in the head-up position. When the subjects gave signs of cerebral anoxia (which varied from fainting and dizziness to violent convulsions) the range of fall of the mean arterial pressure was 21 to 64 per cent, and that of the cerebral blood flow 16 to 47 per cent. However, it is possible that anesthetized patients may have a better tolerance for cerebral anoxia than conscious subjects. Wechsler et al.[56] showed in patients anesthetized with barbiturates that the oxygen consumption of the brain is only 2.1 cc. per 100 gm. per minute, as compared with 3.3 cc. in conscious subjects. Rollason,[195] in a review article, cited a report that slowing of the alpha rhythm of the electroencephalogram occurred when the systolic pressure was lowered to 50. Schallek and Walz,[196] studying the electroencephalograms in anesthetized dogs during hypotension induced with Arfonad and hexamethonium, found that the electroencephalogram was not altered even when the systolic pressure reached 40 if the rate of fall of arterial pressure was slow (1 to 10 per minute); if the rate of fall was fast there was a depression or flattening of the waves of the electroencephalogram. Therefore, from all these observations, a critical level of arterial pressure for adequate blood supply and oxygenation of the brain still cannot be determined. On the basis of these investigations and of previous clinical experience it is suggested that hypotensive anesthesia should not be used in patients with hypertension and arteriosclerosis. The arterial pressure should not be lowered to extreme levels or too fast if cerebral damage is to be avoided.

The changes in renal function during induced hypotension were studied in man by several groups of investigators.[50,197-201] It was a consistent finding that the drop in arterial pressure was accompanied by a concomitant fall of the glomerular filtration rate and effective renal plasma flow in conscious subjects. The urine flow and electrolyte excretion were also depressed. These changes were more marked in patients

with renal damage.[197] Moyer and Mills[200,201] also stated that the decrease in glomerular filtration rate was not due to a decrease in the number of functioning units, since the maximum tubular function as measured by PAH clearance (TmPAH) was not altered. Miles et al.[50] studied the effect of pentamethonium on renal circulation during anesthesia in man. In the presence of a reduced renal blood flow and glomerular filtration rate during anesthesia the administration of pentamethonium lowered the arterial pressure but did not alter the renal blood flow. This was interpreted as the result of substantial renal vasodilatation from the pentamethonium.

Changes of the splanchnic circulation are similar to those of the renal circulation. Reynolds and his associates[202] measured the splanchnic blood flow, splanchnic vascular resistance and oxygen consumption in 17 conscious subjects before and after the injection of 1 mg. of hexamethonium per kilogram of body weight. They found that the estimated splanchnic blood flow fell in proportion to the reduction of arterial pressure. The splanchnic vascular resistance, hepatic glucose output and arterial glucose and lactic acid concentrations were not changed significantly. The splanchnic oxygen consumption was not altered with an increase of the arterial hepatic venous oxygen difference. Bromage,[203] reporting the gross appearance of the liver during hypotensive anesthesia in 17 patients, stated that a systolic pressure of 60 to 70 was critical for the maintenance of normal color and consistence of the liver; below that level the liver became turgid and rubbery to touch and slate gray in color. Thus, the presence of renal and hepatic damage contraindicates the use of hypotensive anesthesia.

Besides the possibility of damaging the vital organs, the use of methonium compounds has a few other drawbacks. The circulatory response cannot be predicted, and quite often hypotension cannot be obtained. Once the hypotension has been reversed with vasopressor amines subsequent attempts to lower the arterial pressure are difficult.[204] Since the vascular compensatory mechanisms are obliterated by the ganglionic block the response to vasopressor drugs is often exaggerated.[205] Reactionary hemorrhage in the operative site, as a result of a sudden, marked rise in arterial pressure, can be bothersome and serious. In short, the hypotension induced with methonium compounds is not controllable.

Randall et al.[206] studied the action of another compound capable of producing hypotension of short duration. It is a thiophanium derivative (*d*-3,4 [1′,3′-dibenzyl-2′-keto-imidazolido]-1,2-trimethylene thiophanium *d* camphor sulfonate, RO2-2222) with a trade name of Arfonad. It has characteristic ganglionic blocking and hypotensive effects in laboratory animals. McCubbin and Page[207] studied the action of Arfonad in dogs and concluded that it lowered the arterial pressure primarily by its direct vasodilating effect. They showed that its hypotensive action was not diminished by spinal-cord transection at the sixth cervical segment or sympathectomy. Direct intra-arterial injection caused severe vasodilatation in the perfused denervated leg. Arfonad is used clinically as a continuous intravenous drip to induce hypotension during anesthesia. Preliminary reports[204,208-210] indicate that this agent may be superior to methonium compounds for inducing hypotension because of its short action and better controllability. With the 0.1 per cent solution the desired arterial pressure level is reached and maintained by adjustment in the rate of infusion. When the infusion is discontinued the arterial pressure usually returns to the control level within twelve to fifteen minutes. The use of vasopressors is therefore not necessary. The hemodynamic changes during induced hypotension and their effects on vital organs also apply to Arfonad, and the contraindications should be the same as those for the methonium compounds.

In conclusion it can be stated that induced hypotension may be a dangerous procedure. Only with definite indications can its clinical application be justified, and then only when there is no contraindication.

The anesthesiologist who intentionally reduces the patient's arterial pressure should be aware of its possible dangers and try to keep the systolic arterial pressure above a safe level of 80. He must also maintain adequate ventilation and replace any blood loss that may occur. (It has been shown that patients with induced hypotension tolerate blood loss very poorly.[211]) Finally, the duration of the induced hypotension should not be unduly prolonged.

Problems of Pain and Analgesics

The search for new analgesics has been continued throughout the years. A number of new synthetic agents and morphine derivatives were shown to possess promising analgesic potency in laboratory animals as well as in man. However, the final judgment of their clinical value for the relief of pain must depend not only on their analgesic potency but also on the frequency of untoward side effects and habit-forming potentialities with continuous usage. The question of evaluating analgesic action in human subjects is difficult because of the complexity of the problem of pain itself. Subjective reaction to a painful stimulus can vary greatly. Factors such as emotion, psychic suggestions and physical status all modify subjective reaction so that a noxious stimulus may not be perceived at all, or may cause, conversely, enhancement of suffering.

Since Hardy, Wolff and Goodell[212] devised a technic for quantitative measurement of the thermal pain threshold and pain intensity, the method or its modifications have been extensively investigated to determine the potency of various analgesic agents. Wolff, Hardy and Goodell[213] have used this method to study the analgesic potency of morphine, methadon, codeine

and related compounds. Other investigators,[214-218] with the same technic, could not reproduce the findings of Hardy and his co-workers.

Postoperative pain offers good possibilities for the evaluation of analgesics. Unfortunately, the use of this type of clinical pain also has serious pitfalls. Papper, Brodie and Rovenstine[219] showed that significant pain is present in approximately a third of patients subjected to a variety of operations. One third of these patients have no significant pain and do not require potent analgesics. Keats and Beecher[220] observed that pentobarbital, in a dose of 90 mg. per 70 kg. of body weight, can relieve postoperative pain in 50 per cent of cases, presumably by psychic influence, and that a placebo injection of saline solution also relieves suffering in 20 per cent of cases, apparently as the result of suggestion. It is obvious, then, that placebo reactors must be excluded when postoperative pain is used in the study of analgesics.

Beecher and his co-workers[221-226] studied postoperative pain in a large number of patients and with a rigidly controlled "double blind" method. The drug given was unknown both to the patient and to the person who evaluated the patient's response, which was classified as "relief" (absence of pain) or "no relief." The validity of this method was tested with a known morphine solution against an unknown morphine solution.[224] It was found that analgesic potency of 10.8 mg. of the unknown morphine was equal to that of 10 mg. of the standard morphine. Therefore, in spite of the complexity of the problem, this method should be considered acceptable for the study of analgesics.

With this method Beecher and his co-workers have evaluated the analgesic potency of a number of agents. Their results, as compared with morphine, are summarized in Table 1.

TABLE 1. *Analgesic Potency of Various Drugs.*

DRUG	DOSAGE REQUIRED FOR RELIEF OF PAIN *mg./70 kg. of body wt.*
Morphine	10
1-methadone	4–6
l-d-methadone	10
1-isomethadone	10
1-d-isomethadone	25–35
Heptazone	50–60
6-methyldihydromorphine	30
Metapon	3

Studies of the side actions of these agents were carried out on healthy adults.[223,226] All these agents, except for 1-isomethadone, when used in comparable analgesic doses, are likely to have side actions similar in incidence and duration to those from morphine. 1-Isomethadone in equipotent doses produced fewer signs and symptoms, especially nausea and vomiting, than the others. However, the intensity of respiratory depression was the same as that with morphine.

Another new synthetic morphine analogue was introduced into clinical medicine in 1949. It was synthetized by Schnider and Grussner[227] and named Dromoran, with the chemical formula of 3-hydroxy-N-methyl morphinan hydrobromide. It was used by several groups for the relief of clinical pain from cancer or after operations.[228-231] Dromoran in a dosage of 5 mg. gave the same amount of relief as 10 mg. of morphine. Keutmann and Foldes[231] claimed that it caused fewer side actions, especially nausea and vomiting, but since the evaluation of the side effects was made on postoperative patients, such a conclusion may be questionable.

It is evident from the foregoing, in spite of the large numbers of new morphine derivatives made and tested for analgesic action and side-action liability, that none of them possess any outstanding advantage over morphine. However, minor advantages of various drugs can be exploited to manage clinical situations under various circumstances.

A new morphine derivative, n-allyl-nor-morphine, that has the unique action of counteracting the actions of morphine and its related compounds has been developed.[232] This drug does not increase the pain threshold in laboratory animals, but when given before or after the administration of morphine, Methadon, Heptazone and meperidine it prevents a rise in pain threshold or returns the elevated threshold to prenarcotic levels.[233] It also counteracts the respiratory-depressant effects of the narcotics and protects animals from lethal doses of these agents. Clinically, in doses of 5 to 10 mg. given intravenously, it is effective against morphine and meperidine narcosis. The peak action is reached one or two minutes after the injection. The average duration of action is about an hour. In human subjects n-allyl-nor-morphine can cause respiratory depression and a fall in blood pressure. It has no antagonistic action against barbiturates, ether or cyclopropane depression.[234] In animals and in man injection into the mother or fetus just before, or shortly after, delivery protects the fetus from the depression of morphine derivatives.[235] The site of action of n-allyl-nor-morphine has not been clearly defined. It has been speculated that the drug is a nonspecific antagonist of morphine, or that it has a competitive action for the receptor site.[236] Whatever the mechanism of action it is a useful therapeutic agent in the therapy of depression from the effects of morphine and its related compounds.

SUMMARY

Developmental advances in anesthesiology during the last decade are outlined largely in the direction of studies designed to elucidate basic mechanisms of the anesthetized state. Progress in understanding the physiologic derangements occurring during anesthesia has been made. It appears noteworthy, as a sign of the interests in this field, that work in the development of new drugs has not been so important as the efforts to understand the old ones more completely.

References

142. Apgar, V. Proposal for new method of evaluation of newborn infant. *Anesth. & Analg.* **32**:260-267, 1953.
143. Apgar, V., McIntosh, R., Taylor, H. C., Day, R., and Girdany, B. Unpublished data.
144. Day, R., Goodfellow, A. M., Apgar, V., and Beck, G. J. Pressure-time relations in safe correction of atelectasis in animal lungs. *Pediatrics* **10**:593-602, 1952.
145. Bloxsom, A. Asphyxia neonatorum: new method of resuscitation. *J.A.M.A.* **146**:1120-1124, 1951.
146. Apgar, V., and Kreiselman, J. Studies on resuscitation: an experimental evaluation of Bloxsom air lock. *Am. J. Obst. & Gynec.* **65**:45-52, 1953.
147. Brodie, B. B., et al. Fate of thiopental in man and method for its estimation in biological material. *J. Pharmacol. & Exper. Therap.* **98**:85-96, 1950.
148. Mark, L. C., Papper, E. M., Brodie, B. B., and Rovenstine, E. A. Quantitative pharmacologic studies with Pentothal. *New York State J. Med.* **49**:1546-1549, 1949.
149. Brodie, B. B., Burns, J. J., Lief, P. A., and Papper, E. M. Intravenous anesthetics — new concepts. I. Experimental aspects. *Anesth. & Analg.* **31**:145-147, 1952.
150. Brodie, B. B., Bernstein, E., and Mark, L. C. Role of body fat in limiting duration of action of thiopental. *J. Pharmacol. & Exper. Therap.* **105**:421-426, 1952.
151. Bollman, J. L., Brooks, L. M., Flock, E. V., and Lundy, J. S. Tissue distribution with time after single intravenous administration of Pentothal sodium (sodium ethyl (1-methylbutyl) thiobarbiturate) and Pentothal S^{35}. *Anesthesiology* **11**:1-7, 1950.
152. Shideman, F. E., Gould, T. C., Winters, W. D., Peterson, R. C., and Wilner, W. K. Distribution and *in vivo* rate of metabolism of thiopental. *J. Pharmacol. & Exper. Therap.* **107**:368-378, 1953.
153. Taylor, J. D., Richards, R. K., and Tabern, D. L. Metabolism of S^{35} thiopental (Pentothal): chemical and paper chromatographic studies of S^{35} excretion by rat and monkey. *J. Pharmacol. & Exper. Therap.* **104**:93-102, 1952.
154. Tabern, D. L., Taylor, J. D., and Gleason, G. I. Radioisotopes in pharmaceutical and medical studies. II. *Nucleonics* **7**:40-55, 1950.
155. Richards, R. K., and Appel, M. Barbiturates and liver. *Anesth. & Analg.* **28**:64-77, 1941.
156. Scheifley, C. H., and Higgins, G. M. Effect of partial hepatectomy on action of certain barbiturates and phenylurea derivative. *Am. J. M. Sc.* **200**:264-268, 1940.
157. Scheifley, C. H. Pentothal sodium: its use in presence of hepatic disease. *Anesthesiology* **7**:263-267, 1946.
158. Masson, G., and Belsdell, E. Influence of liver and kidney on duration of anesthesia produced by barbiturates. *Anesthesiology* **6**: 483-491, 1945.
159. Lundy, J. S., and Adams, R. C. Intravenous anesthesia. *Anesthesiology* **1**:145-152, 1940.
160. Dorfman, A., and Goldbaum, L. R. Detoxification of barbiturates. *J. Pharmacol. & Exper. Therap.* **90**:330-337, 1947.
161. Shideman, F. E., Kelly, A. R., and Adams, B. J. Role of liver in detoxication of thiopental ((Pentothal) and two other thiobarbiturates. *J. Pharmacol. & Exper. Therap.* **91**:331-339, 1947.
162. Kelly, A. R., Adams, B. J., and Shideman, F. E. Role of liver in detoxication of thiopental (Pentothal) and certain other thiobarbiturates. *Federation Proc.* **6**:344, 1947.
163. Kelly, A. R., and Shideman, F. E. Liver as major organ involved in detoxication of thiopental by dog. *Federation Proc.* **8**:306, 1949.
164. Shideman, F. E. *In vitro* metabolism of barbiturates. *Federation Proc.* **11**:640-646, 1952.
165. Shideman, F. E., Kelly, A. R., Lee, L. E., Lowell, V. F., and Adams, B. J. Role of liver in detoxication of thiopental (Pentothal) by man. *Anesthesiology* **10**:421-428, 1949.
166. Richards, R. K., Taylor, J. D., and Kueter, K. E. Effect of nephrectomy on duration of sleep following administration of thiopental and hexobarbital. *J. Pharmacol. & Exper. Therap.* **108**: 461-473, 1953.
167. Helrich, M., Papper, E. M., and Rovenstine, E. A. Surital sodium: new anesthetic agent for intravenous use: preliminary clinical evaluation. *Anesthesiology* **11**:33-40, 1950.
168. Bornette, W. L., and Tuohy, E. B. Clinical trial of Surital sodium in 1200 cases of general anesthesia. *Anesth. & Analg.* **30**: 159-166, 1951.
169. Stephen, C. R., and Martin, R. Clinical experience with Surital sodium in anesthesia. *North Carolina M. J.* **12**:501-504, 1951.
170. Littlefield, P. A., Stoelting, V. K., and Graf, J. P. Clinical evaluation of Surital sodium, new intravenous barbiturate: report of 1000 cases. *J. Indiana M. A.* **44**:1105-1109, 1951.
171. Clarke, M. T., Walton, G. H., and Bewersdorf, H. L. Clinical experience with Surital sodium: preliminary report. *Anesth. & Analg.* **31**:73-86, 1952.
172. Phillips, H. S. Some clinical observations on use of Surital sodium in combination anesthesia. *Anesth. & Analg.* **32**:56-61, 1953.
173. Cassington, H. G., and Raventos, J. Kemithal: new intravenous anesthetic. *Brit. J. Pharmacol.* **1**:215-224, 1946.
174. Brodie, B. B. Physiological disposition and chemical fate of thiobarbiturates in body. *Federation Proc.* **11**:632-639, 1952.
175. Swanson, E. E., and Chen, K. K. Ultra-short-acting thiobarbituric acids. *Proc. Exper. Biol. & Med.* **82**:212-215, 1953.
176. Peterson, R. C., et al. Study of certain N-alkyl thiobarbiturates. *Federation Proc.* **12**:356, 1953.
177. Lief, P. A., Burns, J. J., Papper, E. M., and Brodie, B. B. Intravenous anesthesia — new concepts. II. Clinical aspects. *Anesth. & Analg.* **31**:147-150, 1952.
178. Gardner, W. J. Control of bleeding during operation by induced hypotension. *J.A.M.A.* **132**:572-574, 1946.
179. Griffiths, H. W. C., and Gillies, J. Thoraco-lumbar splanchnicectomy and sympathectomy: anaesthetic procedure. *Anaesthesia* **3**: 134-146, 1948.
180. Paton, W. D. M., and Zaimis, E. J. Pharmacological actions of polymethylene bistrimethylammonium salts. *Brit. J. Pharmacol.* **4**:381-400, 1949.
181. Davison, M. H. A. Case against hypotension. *Anaesthesia* **8**:255-262, 1953.
182. Hampton, L. J., and Little, D. M., Jr. Results of questionnaire concerning controlled hypotension in anaesthesia. *Lancet* **1**:1299, 1953.
183. *Idem.* Complications associated with use of "controlled hypotension" in anesthesia. *Arch. Surg.* **67**:549-556, 1953.
184. Rakita, L., and Sancetta, S. M. Acute hemodynamic effects of hexamethonium in normotensive man. *Circulation Res.* **1**:499-501, 1953.
185. Grob, D., and Langford, H. G. Further observations on effects of autonomic blocking agents in patients with hypertension. II. Hemodynamics, ballistocardiographic and electrocardiographic effects of hexamethonium and pentamethonium. *Circulation* **8**:352-369, 1953.
186. Grob, D., Scarborough, W. R., Kattus, A. A., Jr., and Langford, H. G. Further observations on effects of autonomic blocking agents in patients with hypertension. II. Hemodynamics, ballistocardiographic and electrocardiographic effects of hexamethonium and pentamethonium. *Circulation* **8**:352-369, 1953.
187. Shackman, R., Graber, I. G., Melrose, D. G., and Smith, J. Haemodynamics of methonium hypotension during anaesthesia. *Anaesthesia* **7**:217-222, 1952.
188. Murphy, Q. R., et al. Effect of hexamethonium bromide (C-6) on cardiovascular system in normotensive and hypertensive dogs. *Federation Proc.* **12**:101, 1953.
189. Gillmon, H. R., Kopelman, H., McMichael, J., and Milne, I. G. Effect of hexamethonium bromide on cardiac output and pulmonary circulation. *Lancet* **2**:898-902, 1952.
190. Kety, S. S., King, B. D., Horrath, S. M., Jeffers, W. A., and Hafkenschiel, J. H. Effects of acute reduction in blood pressure by means of differential spinal sympathetic block on cerebral circulation of hypertensive patients. *J. Clin. Investigation* **29**:402-407, 1950.
191. Nilsson, E. Application of method for investigation of cerebral damage following anaesthesia using controlled hypotension — preliminary communication. *Brit. J. Anaesth.* **25**:24-31, 1953.
192. Ngai, S. H., and Nelson, E. C. Unpublished data.
193. Morris, G. C., Jr., Moyer, J. H., Snyder, H. B., and Haynes, B. W., Jr. Vascular dynamics in controlled hypotension: study of cerebral and renal hemodynamics and blood volume changes. *Ann. Surg.* **138**:700-711, 1953.
194. Finnerty, F. A., Jr., Witkin, L., and Fazekas, J. F. Acute hypotension and cerebral hemodynamics: preliminary report: *M. Ann. District of Columbia* **22**:115, 1953.
195. Rollason, W. N. Anesthesia and "bloodless" field. *Anesth. & Analg.* **32**:289-304, 1953.
196. Schalkek, W., and Walz, D. Unpublished data.
197. McQueen, E. G. Hexamethonium bromide and kidney function. *M.J. Australia* **1**:769-771, 1952.
198. MacKinnon, J. Effect of hypotension-producing drugs on renal circulation. *Lancet* **2**:12-15, 1952.
199. Haugen, H. N., and Blegen, E. M. Renal response to hexamethonium. *Scandinav. J. Clin. & Lab. Invest.* **5**:58-62, 1953.
200. Moyer, J. H., and Mills, L. C. Hexamethonium — its effect on glomerular filtration rate, maximal tubular function, and renal excretion of electrolytes. *J. Clin. Investigation* **32**:172-184, 1953.
201. Mills, L. C., and Moyer, J. H. Acute effects of hexamethonium on renal hemodynamics in normotensive and hypertensive human subjects. *Am. J. M. Sc.* **226**:1-15, 1953.
202. Reynolds, T. B., Paton, A., Freeman, M., Howard, F., and Sherlock, S. Effect of hexamethonium bromide on splanchnic blood flow, oxygen consumption and glucose output in man. *J. Clin. Investigation* **32**:795-800, 1953.
203. Bromage, P. R. Effect of induced vascular hypotension on liver: alterations in appearance and consistence. *Lancet* **2**:10-12, 1952.
204. Anderson, S., and McKissock, W. Controlled hypotension with Arfonad in neurosurgery: with special reference to vascular lesions. *Lancet* **2**:754-757, 1953.
205. Finnerty, F. A., Jr., and Freis, E. D. Experimental and clinical evaluation in man of hexamethonium (C 6), new ganglionic blocking agent. *Circulation* **2**:828-836, 1950.
206. Randall, L. O., Peterson, W. G., and Lehmann, G. Ganglionic blocking action of thiophanium derivatives. *J. Pharmacol. & Exper. Therap.* **97**:48-57, 1949.
207. McCubbin, J. W., and Page, I. H. Nature of hypotensive action of thiophanium derivative (RO2-2222) in dogs. *J. Pharmacol. & Exper. Therap.* **105**:437-442, 1952.
208. Nicholson, M. J., Sarnoff, S. J., and Crehan, J. P. Intravenous use of thiophanium derivative (Arfonad-RO2-2222) for production of flexible and rapidly reversible hypotension during surgery. *Anesthesiology* **14**:215-225, 1953.
209. Sadove, M. S., Wyant, G. M., and Gleave, G. Controlled hypotension: study on Arfonad (RO2-2222). *Anaesthesia* **8**:175-181, 1953.
210. Magill, I. W., Scurr, C. F., and Wyman, J. B. Controlled hypotension by thiophanium derivative. *Lancet* **1**:219, 1953.
211. Enderby, G. E. H., and Davison, M. H. A. Discussion on use of hypotensive drugs in surgery. *Proc. Roy. Soc. Med.* **44**:829-840, 1951.
212. Hardy, J. D., Wolff, H. G., and Goodell, H. Studies on pain: new method for measuring pain threshold: observations on spatial summation of pain. *J. Clin. Investigation* **19**:649-657, 1940.
213. Wolff, H. G., Hardy, J. D., and Goodell, H. Studies on pain: measurement of effect of morphine, codeine and other opiates on pain threshold and analysis of their relation to pain experience. *J. Clin. Investigation* **19**:659-680, 1940.
214. Thorp, R. H. Assessment of analgesic activity in new synthetic drugs. *Brit. J. Pharmacol.* **1**:113-126, 1946.
215. Beecher, H. K., and Bromage, R. R. Human pain thresholds determined by radiant heat technique and effect upon them of acetylsalicylic acid, morphine sulfate and sodium phenobarbital. *J. Pharmacol. & Exper. Therap.* **101**:47-55, 1951.
216. Jackson, H. Effect of analgesic drugs on sensation of thermal pain in man. *Brit. J. Pharmacol.* **7**:204-214, 1952.
217. Haugen, F. P., and Livingston, W. K. Experiences with Hardy–Wolff–Goodell dolorimeter. *Anesthesiology* **14**:109-116, 1953.
218. Beecher, H. K., Hardy, J. D., Wolff, H. G., and Goodell, H. Pain—controlled and uncontrolled. *Science* **117**:164-167, 1953.
219. Papper, E. M., Brodie, B. B., and Rovenstine, E. A. Postoperative pain: its use in comparative evaluation of analgesics. *Surgery* **32**:107-109, 1952.

220. Keats, A. S., and Beecher, H. K. Pain relief with hypnotic doses of barbiturates and hypothesis. *J. Pharmacol. & Exper. Therap.* **100**:1-13, 1950.
221. Denton, J. E., and Beecher, H. K. New analgesics. I. Methods in clinical evaluation of new analgesics. *J.A.M.A.* **141**:1051-1057, 1949.
222. *Idem.* New analgesics. II. Clinical appraisal of narcotic power of methadone and its isomers. *J.A.M.A.* **141**:1146-1148, 1949.
223. *Idem.* New analgesics. III. Comparison of side effects of morphine, methadone and methadone's isomers in man. *J.A.M.A.* **141**: 1148-1153, 1949.
224. Keats, A. S., Beecher, H. K., and Mosteller, F. C. Measurement of pathological pain in distinction to experimental pain. *J. Appl. Physiol.* **3**:35-44, 1950.
225. Keats, A. S., and Beecher, H. K. Analgesic activity and toxic effects of acetylmethadol isomers in man. *J. Pharmacol. & Exper. Therap.* **105**:210-215, 1952.
226. *Idem.* Analgesic potency and side action liability in man of Heptazone, WIN 1161-2, 6-methyl dihydromorphine, Metopon, levoisomethadone and pentobarbital sodium, as further effort to refine methods of evaluation of analgesic drugs. *J. Pharmacol. & Exper. Therap.* **105**:109-129, 1952.
227. Schneider, O., and Grussner, A. Synthese von oxy-morphinanen. *Helvet. chim. acta* **32**:821-828, 1948.
228. Junkerman, C. L., Heen, R. C., and Pohle, H. W. Clinical experience with new analgesic agent. *J. Lab. & Clin. Med.* **34**: 1615, 1949.
229. Tidrick, R. T., Zager, L. I., Eastwood, W. D., Wilkins, D. S., and Jaggard, R. S. Control comparison of NU-2206 (3-hydroxyl-N-methyl morphinan hydrobromide) with morphine sulfate for relief of postoperative pain. *J. Lab. & Clin. Med.* **34**:1758, 1949.
230. Zager, L. L., Sawtelle, W. W., Gross, E. G., Nagly, S. F., and Tidrick, R. T. Observations on use of new analgesic, NU 2206 (3-hydroxy-N-methylmorphinan hydrobromide). *J. Lab. & Clin. Med.* **34**:1530-1537, 1949.
231. Keutmann, E., and Foldes, F. F. Analgesic effect of dromoran hydrobromide (3-hydroxy-N-methyl morphinan hydrobromide) in postoperative pain. *New Eng. J. Med.* **244**:286-288, 1951.
232. Huggins, R. A., Glass, W. G., and Bryan, A. R. Protective action of N-allyl-normorphine against respiratory depression produced by some compounds related to morphine. *Proc. Soc. Exper. Biol. & Med.* **75**:540, 1950.
233. Smith, C. C., Lehman, E. G., and Gilfillan, J. L. Antagonistic action of N-allyl-normorphine upon analgesic and toxic effects of morphine, methadone derivatives and isonipecaine. *Federation Proc.* **10**:335, 1951.
234. Eckenhoff, J. E., Hoffman, G. L., and Dripps, R. D. N-allylnormorphine: antagonist to opiates. *Anesthesiology* **13**:242-251, 1952.
235. Snyder, F. F. Action of N-allyl-normorphine during labor. *Federation Proc.* **12**:136, 1953.
236. Eckenhoff, J. E., Elder, J. D., and King, B. D. N-allyl-normorphine in treatment of morphine or demerol narcosis. *Am. J. M. Sc.* **223**:191-197, 1952.

MEDICAL INTELLIGENCE

BY THE LONDON POST

Sport and Medicine — The New Epidemiology — In Praise of Tobacco

JOHN LISTER, M.D.

LONDON, ENGLAND

IT was a proud day for Britain and for the medical profession when Roger Bannister accomplished at Oxford what a whole world of milers have recently been bracing themselves to achieve first — the four-minute mile. As a physiologist and a medical student Bannister has a clear insight into the medical aspects of violent physical exertion. It is now generally agreed that strenuous exertion has no immediate ill effect on the healthy body, but it is more difficult to assess the delayed effects of exercises. Increased heart size is commonly found in men taking part in sports that entail long-continued exertion, but Sir Adolphe Abrahams *(Lancet* **1**:1133 and 1187, 1951) has shown that when death occurs during physical exertion the effort is frequently trivial and some pre-existing but unsuspected lesion is usually revealed.

Sir Alan Rook, senior health officer to Cambridge University, recently carried out an investigation to determine the long-term effects of exercise *(Brit. M. J.* **1**:773, 1954). He studied the longevity and, when possible, the cause of death in three groups of men who entered the University between the years 1860 and 1900. The first group comprised 834 sportsmen who were athletes, cricketers, rowing men and rugby footballers. The other two groups made up the control subjects and consisted of 382 intellectuals, whose names were taken from the honors' list of the Historical Register of the University, and 379 undergraduates chosen at random but who were not distinguished either intellectually or in the field of sport. The results of this investigation gave no evidence that the sportsmen died earlier than the group chosen at random and, although the intellectuals lived an average of a year and a half longer, this small difference was not significant. Furthermore, there was no evidence that cardiovascular causes of death were more prominent or occurred at an earlier age among the sportsmen.

In a leading article the *British Medical Journal* rejoiced in these findings, for they would seem to permit the young at least one form of indulgence in which there is so far no statistical reason for restraint. They may row in boats if they wish, but those who prefer to crowd the towpath can take comfort from the knowledge that it makes little difference to their expectation of life whether they are on the bank or in the boats.

Bannister himself, writing in a Symposium on Stress (*Practitioner* **172**:63, 1954), admits that sport imposes stresses on both mind and body and agrees that sportsmen are exposed to incidental risks. A man well known for his sporting prowess may enjoy living dangerously and may be tempted to indulge in athletic exercise unsuitable for his age. He claims, however, that athletes tend to be well adjusted people. Their adaptation to the stresses of sport makes them resilient, and their experience of success and failure gives them a good sense of proportion about themselves. He concludes with the stimulating thought that playing a game is a more uninhibited outlet than watching it.

* * *

There was a lively atmosphere at a recent congress of the Royal Sanitary Institute when the problem of epidemiology was discussed. The president of the con-

gress, Lord Feversham, pointed out that many modern sickness problems are created by emotional stress and worry rather than by germs. Professor John Gordon, of Harvard University, spoke of epidemiology as a method of study evolved in recurrent outbreaks of bacterial infection. The new epidemiology should not be restricted to epidemics and infectious disease but should be adapted to combat such afflictions as cancer, mental illness and accidents. He maintained that bad luck serves no better as an explanation of injury than demons did as the cause of disease. He believed that the new epidemiology should be regarded as the diagnostic discipline of public health and not as a body of knowledge too frequently restricted to epidemics and communicable disease. Taking up this theme, one forthright speaker declared that it is a stupendous fallacy to assume that the control, prevention and cure of infectious disease consist merely in the eradication of the causative organisms and urged that the public-health service should broaden its horizon and break away from its bondage to bacteriology. He also suggested that too much emphasis is placed on the statistical approach. He agreed that the curve of mortality from lung cancer follows closely the curve of the rise in tobacco consumption, but he asked, perhaps facetiously, whether it would be inopportune to point out that the curve of all types of cancer follows closely the curve of the increased consumption of margarine over the last fifty years and also that a similar curve is shown in the rise in membership of one of the two great political parties. This heretical viewpoint was challenged by a statistician from the Registrar General's Office, who argued that mortality and morbidity records are valuable pointers to direct field research into the most useful channels. He claimed that changes and local variations in these statistics are of increasing importance now that epidemiology is turning from short-term epidemics, when the results of control measures are quickly apparent, to investigations in which the time factor is a blunted instrument.

* * *

The *Manchester Guardian* has offered words of great comfort for the inveterate smoker. It appears that the recent indictment of smoking by the Advisory Committee on Cancer is little more than the latest contribution to a long and inconclusive debate. As long ago as 1595 there appeared a publication entitled "The Opinion of the Late and Best Phisitions Concerning Tobacco," and in 1603 James I followed this up with a treatise called "A Counterblast to Tobacco." At that time, however, there were those who spoke in favor of the herb. Thus, in 1588, Thomas Harriott presented his "Brief and True Report of the New Found Land of Virginia" and spoke of the many rare and wonderful proofs of the beneficial effects of the tobacco plant. Harriott claimed that it opened the pores and passages and purified the body and preserved it from many diseases common to England. Furthermore, in those days tobacco was obtainable from apothecaries' shops in London, and clients were encouraged to consume it on the premises and exhale the smoke through their nostrils so that the widest possible circulation through the head was obtained. It was, however, during the Great Plague of 1665 that tobacco gained its greatest reputation as a prophylactic. Indeed, Pepys records that he bought some "roll tobacco to smell to and to chaw" to allay his fears on seeing the plague-crossed houses of Drury Lane. At this time, too, it was even said that the scholars of Eton College were encouraged to take tobacco daily as a disinfectant. In fact its use as a disinfectant still survives, and even today there are those who claim that the infusion of tobacco is an excellent germicide and the juice from its leaves is occasionally bought as sheep wash.

"MILD MARTYR"

THE following anonymous lines were apparently inspired by the unusual rains this spring:

RAIN

It sometimes seems, this spring, as if the rain
Has fallen more than mortal man can bear.
Incessantly I hark to its refrain
Or watch its slanting passage through the air.
The wind is east again; salty as brine
It thrusts its damp past door and plastered wall,
Smelling of trawler's tubs and tarry twine—
Of coal-tar ointment and of Ichthyol.
Now office hours are over—patients fled,
Dejectedly, with wet umbrellas reared—
And still the house calls stretch far out ahead.
Mild martyr, off I start—then mildly cheered
Find sanctuary in a green retreat
Of maples mirrored in a shining street.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 40251

PRESENTATION OF CASE

First admission. A fifty-nine-year-old service manager entered the hospital complaining of "high blood pressure and nervousness."

About a year previously he began to have dizzy spells and was examined by his family physician, who found the blood pressure to be "about 230" and also found albuminuria. He was treated with hypotensive drugs and placed on a diet with "no added salt," and although the blood pressure was allegedly reduced, the symptoms increased and nervousness, easy fatigability and lethargy developed. He lost 52 pounds in that year. Six months later he had an episode of severe epistaxis and was advised to sleep on two pillows. At about the same time he began to note dyspnea on climbing one flight of stairs. For six or seven weeks before admission he had nocturnal attacks, which awakened him suddenly, caused dry coughing and shortness of breath and were relieved by whisky. Three weeks before admission he was placed on digitalis, "one tablet a day," but did not improve and stopped this after a week. He denied pain, ankle edema and unconsciousness. He had occasional "skipped beats" and had had epigastric "gnawing" for about six months that came on fifteen minutes after meals and was not relieved by antacids but was relieved by bread and milk.

The patient had had "rheumatic fever and typhoid fever" simultaneously at the age of ten, with joint pains and extreme weakness lasting about six months. He was carried about bodily at that time and was allegedly dropped on one occasion, with resulting bilateral dislocation of the hips and permanent deformity on the left. Subsequent examination failed to reveal heart murmurs.

Physical examination showed a well nourished man lying flat in bed who had an old deformity of the left hip. Examination of the retina demonstrated ++++ arteriovenous nicking with some exudate and without papilledema. The neck veins were not distended, and the thyroid gland was not enlarged. The chest was increased in anteroposterior diameter, and bilateral basal rales were heard. The heart was enlarged, the border of dullness extending 2 cm. to the left of the midclavicular and 2 cm. to the right of the midsternal line. There was a Grade 2 blowing systolic murmur to the left of the sternum that was not transmitted. The aortic second sound was of "tambour" quality, and the pulmonic second sound was slightly louder than normal. The liver edge was barely palpable at the right costal border; no other abdominal organs were felt. The prostate was two and a half times the normal size, smooth and not hard.

The temperature was 99.6°F., the pulse 90 and regular, and the respirations 20. The blood pressure was 230 systolic, 130 diastolic.

Routine urinalysis disclosed a specific gravity of 1.010, a ++ to +++ test for albumin, a negative test for sugar and 5 to 8 white cells and occasional granular and hyaline casts per high-power field in the sediment. Examination of the blood revealed a hemoglobin of 12.7 gm. per 100 cc. and a white-cell count of 12,800, with 74 per cent neutrophils. The nonprotein nitrogen was 61 mg., the calcium 9.8 mg., the phosphorus 4.9 mg. and the cholesterol 299 mg. per 100 cc.; the sodium was 125 milliequiv., the potassium 2.8 milliequiv., the chloride 90 milliequiv., and the carbon dioxide 29 milliequiv. per liter. The blood Hinton test was negative. The stools were guaiac negative. The phenolsulfonephthalein excretion was 7 per cent at the end of two hours. The Regitine test was "negative." The basal metabolic rate was +2 per cent. An electrocardiogram demonstrated hypertrophy of the left ventricle, with a possibility of an old posterior infarct. X-ray films of the chest showed the heart to be enlarged, particularly the left ventricle, with some enlargement of the atrium. There was a minimal amount of fluid in the left pleural cavity. Pulmonary vascular congestion was present without definite pulmonary edema (Fig. 1). An intravenous pyelogram disclosed faint visualization of the right kidney in twenty minutes and no excretion on the left; there was a small stone in the right kidney. A gastrointestinal series and barium-enema examination were negative except for diverticulosis of the colon.

The patient was digitalized, given mercurial diuretics and ammonium chloride and placed on a diet containing 500 mg. of sodium. He improved and was discharged to a nursing home.

Final admission (three and a half weeks later). After discharge he did well and was discharged from the nursing home in two weeks. He was seen in the Out Patient Department, where he was found to be doing so well that mercurial diuretics and ammonium chloride were omitted. Three days before admission he began to have marked dyspnea, weakness, nausea

and orthopnea. A cough productive of brownish sputum without chest pain or chills developed. His family doctor gave him "a shot for his water," a "shot for his breathing" and some sleeping pills, without much improvement, and he was readmitted.

Examination showed a pale, somewhat dehydrated, slightly cyanotic man propped up in bed at a 45° sitting position, with the neck veins filled and pulsating. The temperature was 99°F., the pulse 108 and regular, and the respirations 35. The blood pressure was 230 systolic, 140 diastolic. The breath was slightly uremic. The chest was emphysematous, and both leaves of the diaphragm were low. There were generalized inspiratory and expiratory rales and wheezes that made the heart sounds inaudible. One observer found dullness in the left side of the chest posteriorly. The abdomen was protuberant, without fluid. The liver edge was felt about 5 fingerbreadths below the right costal margin and was tender. There was questionable pitting edema of the legs to the knees. There was no calf tenderness. Urinalysis again revealed a ++ to +++ test for albumin and 5 to 10 white cells, 3 to 6 red cells and occasional granular casts per high-power field in the sediment. Examination

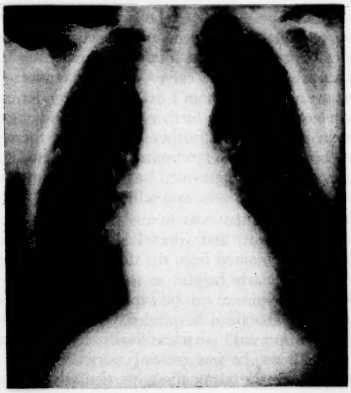


FIGURE 1. *Posteroanterior Film of the Chest, Showing Cardiac Enlargement, Chiefly of the Left Ventricle, with Evidence of Pulmonary Congestion.*

of the blood disclosed a white-cell count of 12,600, with 90 per cent neutrophils, a hemoglobin of 11 gm. and a hematocrit of 33 per cent. The sodium was 119 milliequiv., the chloride 74 milliequiv., the potassium 4.1 milliequiv., and the carbon dioxide 22 milliequiv. per liter, and the nonprotein nitrogen 120 mg. per 100 cc. An electrocardiogram was consistent with hypertrophy of the left ventricle. There were atrial and ventricular premature beats, and the old posterior infarct was again noted. There was an intermittent cough productive of yellow sputum. A throat culture demonstrated a moderate growth of pneumococci and *Staphylococcus aureus* and abundant alpha-hemolytic streptococci. A chest film showed that the transverse diameter of the heart was 1.5 cm. greater than on the previous examination. The cardiothoracic ratio was 17:28. There was severe pulmonary vascular congestion, with pulmonary edema, more marked on the left, and free fluid in the left pleural cavity, some extending into the major fissure (Fig. 2).

The patient was treated with digitalis, mercurial diuretics, oxygen and tourniquets. He was also placed on penicillin and streptomycin. Fluids were restricted, and he was given 6 per cent saline solution intravenously. On the third hospital day the sodium was 129 milliequiv., the potassium 4.9 milliequiv., the carbon dioxide 20 milliequiv., and the chloride 89 milliequiv. per liter, and the nonprotein nitrogen 223 mg. per 100 cc. He seemed slightly improved. Moist rhonchi were heard at both lung bases, replacing the diffuse fine inspiratory and expiratory rales previously heard. There was slightly decreased aeration in the left axilla. Later the same day the temperature rose to 101°F.; he died quietly during the night.

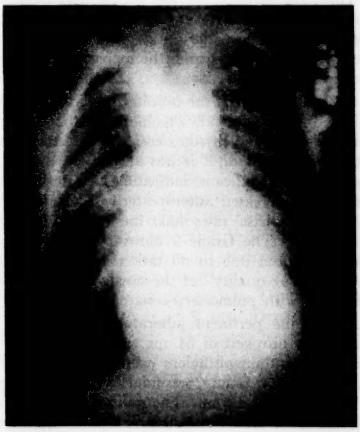


FIGURE 2. *Anteroposterior Roentgenogram of the Chest Taken Four Days before Death, Showing Mottled Densities Throughout Both Lung Fields.*

DIFFERENTIAL DIAGNOSIS

DR. ROBERT S. PALMER*: This hypertensive patient had a weight loss of 52 pounds. If he had said 50 pounds, I should believe the weight lost was perhaps 40 pounds, but since he said 52 pounds, he probably really lost 52 pounds. Such a weight loss is unusual at the age of fifty-nine and makes me think of

*Physician, Massachusetts General Hospital.

cancer or a chronic low-grade infection. Patients who have congestive heart failure for a long time and those with chronic uremia do lose weight, but not that much, in my experience. Elderly people with extensive arteriosclerosis may lose that amount of weight, but usually over a long period. The treatment given before admission — the low-salt diet and digitalis — may have caused loss of appetite and consequent weight loss, but patients usually do not adhere to diets strictly enough to lose this much weight. The epigastric gnawing, since there was serious loss of cardiac reserve, with nocturnal dyspnea, was presumably due to visceral congestion, rather than to a gastrointestinal neoplasm.

The joint pains at the age of ten may have been caused by rheumatic fever or rheumatoid arthritis, or they may have been the result of tuberculosis of the bone. I do not know, from the mere statement, what they were.

On examination in the hospital he did not have an enlarged thyroid gland, which means that he probably did not have thyrotoxicosis. The arteriovenous nicking in the fundi, if it was at a distance from the optic disk, is significant, indicating an arteriolar sclerosis. The increased anteroposterior diameter of the chest and the basal rales make me think he had slight emphysema. The Grade 2 blowing systolic murmur may have been due to dilatation of the heart, and the "tambour quality" of the aortic second sound is consistent with pulmonary congestion.

Among the pertinent laboratory findings are the nonprotein nitrogen of 61 mg. per 100 cc. and the poor phenolsulfonephthalein excretion; he had renal impairment and failure, secondary to heart failure or to primary renal disease. The sodium, potassium and chloride levels indicate electrolyte depletion, although not to a serious degree, that was due to treatment or to the kidney condition. According to Dr. Denovian the Regitine test, if the drug is given intramuscularly, gives a false-negative result in 4 per cent of the cases of pheochromocytomas; if it is given intravenously the percentage of false-negative reactions is even smaller. Pheochromocytomas are so rare and the percentage of false-negative reactions so small that statistically the chance that this patient had a pheochromocytoma is very poor. The possibility of an old posterior infarct, suggested by the electrocardiogram, is only a laboratory suggestion in my mind because there was nothing in the clinical story to go with it.

It was necessary to decide what the process in the kidney was and to determine the cause of the weight loss. If there was chronic vascular disease of the kidneys I should expect them to have been small. The kidney disease may have been infectious, chronic low grade or recurrent, or on the basis of old calculus disease. Other rare conditions to be considered are thrombosis of the main renal vessel or even a malignant tumor of the kidney that wrapped itself around the kidney and the vessels. Such a tumor may cause hypertension. At the time the patient was discharged after the first hospital admission the physicians were wondering about the kidneys, their functional failure and the mild electrolyte depletion. Evidently they decided that the main condition was the heart failure and discharged him on the current, conventional treatment for heart failure: digitalis and the salt-depleting mercurial diuretics and ammonium chloride. The prognosis was very poor because he had hypertension with congestive heart failure and was in renal failure.

Three and a half weeks later he was readmitted to the hospital because something had been added: he suddenly began to have brownish sputum, great increase in cough and shortness of breath. This at once suggests lobar pneumonia or perhaps, more probably, bronchopneumonia. As usual I must also consider pulmonary emboli. One would like to hear of other physical signs: increased tactile fremitus, dullness or flatness and changes in the character of the breathing and voice sounds, permitting a more precise physical diagnosis. The increased size of the liver, which was also noted, may have been related to the new condition in the chest or its effect on the already damaged heart. The absence of calf tenderness may be against pulmonary emboli; perhaps one could have obtained more specific evidence by measuring the calves of the legs at intervals. I must say that I am surprised that the calves were not tender — almost every patient whom I examine has tender calves. The electrolytes were further depleted, and the nonprotein nitrogen was further increased so there may have been a salt-loss syndrome directly related to the kidney disease or aggravated by the treatment or both. The salt loss, however, was still not serious.

While the patient was in the hospital the sputum became purulent, and what I should call a mixed culture was obtained from the throat. Such a culture is not particularly helpful to me. Neither brownish nor purulent sputum can be explained by passive congestion. By the third hospital day he was said to be "slightly improved" — scientifically, that is, because, as we shall see, he was growing worse.

May I see the x-ray films, particularly the intravenous pyelogram?

DR. C. C. WANG: This chest film on the first admission shows considerable enlargement of the heart, chiefly in the region of the left ventricle, and an elongated, somewhat tortuous aorta. There is also prominence of the hilar shadows, some pulmonary congestion on both sides and free fluid in the left pleural cavity. I think the appearance is consistent with cardiac failure (Fig. 1). The chest film taken on the second admission reveals progression of the pulmonary congestion and a somewhat ground-glass appearance of the lung field, suggesting pulmonary edema (Fig. 2).

DR. PALMER: Is there a particular collection of something in the right-upper-lung field?

DR. WANG: There is a localized area of mottled, increased density in the right-upper-lung field; that could represent an infectious process.

DR. PALMER: It could represent pneumonia.

DR. WANG: Yes. The heart shadow is now somewhat larger than previously; there is more fluid in the left pleural cavity and probably some fluid in the left major fissure. The intravenous pyelogram shows the kidney outline to be fairly normal in size and in shape. There are two calcified densities overlying the right midportion of the abdomen. On different projections they appear to lie in the lower pole of the right kidney. After the intravenous injection the contrast material is very poorly excreted from both kidneys; if anything the right functions slightly better than the left.

DR. PALMER: There is not too much difference between them; the excretion is only a little better on the right?

DR. WANG: Yes.

DR. PALMER: And the gastrointestinal series was negative.

DR. WANG: The gastrointestinal series and the Graham test were negative.

DR. PALMER: The kidney shadows look normal, and there is fairly poor renal excretion. From the very poor qualitative tests of kidney function and increase in the nonprotein nitrogen I am surprised that any dye was excreted.

In summary I believe the main diagnoses are hypertension, congestive heart failure, which was progressive and was due to hypertensive heart disease, and coronary-artery disease. The electrocardiogram suggests an old infarction; clinically, there was no impressive evidence for myocardial infarction. The examination of the urine gave evidence of vascular changes in the kidneys. Finally, there was some pulmonary emphysema.

A point that now seems much less important than when I read the protocol is to decide whether the patient had unilateral renal disease and whether the difference in excretion could have been due to thrombosis of the main renal vessel or to a special infection on that side. If the disease was unilateral the physician at some earlier time might have been able to do something about it before it became bilateral, as so many unilateral kidney diseases do. Such calculous disease as was present seems to have been in the lower pole of the kidney on the other side, possibly representing old infection. It is conceivable that the patient had a tuberculous kidney although the clinical course and the findings do not suggest it. I am still left without a good explanation of the marked weight loss if it was not on the basis of chronic, slowly advancing uremia and poor intake of food. The x-ray appearance, with these fair-sized kidneys and only two small stones in the lower pole of one, suggests that he had the end condition that occurs in about 10 per cent of the patients with hypertension — namely, nephrosclerosis and uremia. The great majority of hypertensive patients, about 65 per cent, die from congestive heart failure; approximately 25 per cent have cerebral accidents, of which this man gave no evidence. If he died in uremia with nephrosclerosis he presumably had arteriolar necrosis, in which case he may have had the pathological picture of malignant hypertension, though he did not have the clinical syndrome — namely, papilledema and a rapidly advancing course. Although I have seen malignant hypertension in a patient in the fifties and, I think, in one over sixty it usually occurs in much younger people.

What did he die of? His death was precipitated by a respiratory episode that, because of the purulent and brown sputum, I believe was infection. The x-ray films suggest this, and it looks to me as though he had an extensive patch of bronchopneumonia. This could have been lobar pneumonia in an old, depleted person without the expected leukocytosis, but I shall say that he had bronchopneumonia. I cannot be certain that he did not have pulmonary emboli as well.

A PHYSICIAN: Would you consider that there may have been a glomerulonephritis?

DR. PALMER: It is difficult to predict what the kidneys will show on the basis of the clinical course. To consider glomerulonephritis I should have to hear of intermittent episodes of nondependent edema, particularly at this age, or of such episodes in the past.

DR. BENJAMIN CASTLEMAN: Dr. Denovian, you saw the patient in the Out Patient Department.

DR. JOHN DENOVIAN: I have very little to add to Dr. Palmer's excellent discussion. When I first saw this patient I also thought that the marked hypertension was on a renal basis. Because of the severe azotemia I considered the use of hypotensive drugs contraindicated.

DR. PALMER: Yes; I agree with that.

DR. DENOVIAN: I have no explanation for the weight loss.

DR. PALMER: He was said to be still well nourished after he had lost 52 pounds.

DR. T. HALL: I think the loss of 52 pounds could be explained by the fact that he was placed on a low-sodium diet. He was discharged to a nursing home, where the nurses were strict about the low-salt diet, and he ate almost nothing for the last two weeks of his stay there. For that reason his diet was finally changed to one with no added salt. He was not weighed at the time of the second admission, but I should estimate that his weight was about 130 pounds.

CLINICAL DIAGNOSES

Pulmonary edema.
Hypertensive heart disease.
Nephrosclerosis and azotemia.

DR. ROBERT S. PALMER'S DIAGNOSES

Hypertensive heart disease.

Congestive heart failure.
Coronary-artery disease.
Nephrosclerosis.
Nephrolithiasis.
Uremia.
Bronchopneumonia.

Anatomical Diagnoses

Cardiac hypertrophy, hypertensive type.
Nephrosclerosis, severe.
Bronchopneumonia, severe.
(Uremia.)
Duodenal ulcer, acute.
Nephrolithiasis, right.

Pathological Discussion

Dr. Castleman: The heart was hypertrophied, weighing 650 gm., with a very thick left ventricle but without any changes in the valves—namely, this was cardiac hypertrophy of the hypertensive type. The kidneys were perhaps a little larger than normal—one weighed 180, and the other 210 gm.—and were fairly smooth. Frequently, we find such kidneys in hypertension although they are usually granular and reduced in size. Microscopically, the kidneys showed severe vascular disease, which we would grade 3 or 4, very narrow arterioles, considerable medial hypertrophy and intimal proliferative changes in almost every vessel. There was a small, 4-mm. stone in the right kidney, but there was no evidence of any real pyelonephritis or any other type of renal disease. An occasional arteriole demonstrated medial necrosis, but there was not a widespread arteriolitis such as is found with malignant nephrosclerosis.

The interesting finding was in the lungs. The lungs together weighed 2000 gm., which is over three times the normal size. The right lung was completely solid. On gross inspection the process looked like lobar pneumonia except that at the periphery there were still aerated foci. Similar findings, although not so striking, were present on the left side. Microscopically, there were polymorphonuclear leukocytes in every alveolus, and in some areas the alveolar walls were broken down and abscesses had formed. Many of the bronchioles were filled with pus. The process was a severe confluent bronchopneumonia, with early abscess formation.

An incidental finding, which perhaps reflects the poor state of nutrition, was a very acute duodenal ulcer.

Dr. Lawrence Kunz: Post-mortem culture of the lung revealed the presence of abundant *Haemophilus influenzae,* a moderate amount of *Staph. aureus* and a few beta-hemolytic streptococci and *Escherichia coli.* Except for the *Esch. coli,* which were probably post-mortem contaminants, these results were the same as those of a culture taken the day before the patient died. Of course, the results of the last ante-mortem culture were not available on the ward until the next day.

Dr. Palmer: What I called a mixed throat culture and not helpful to me should have alerted people to what went on.

Dr. Kunz: This appears to be an appropriate occasion to bring up again the problem of the resistant staphylococcus, which has not been mentioned here for some time. The present case appears to me to be that of a pneumococcal pneumonia treated with antibiotics that were efficient in removing the pneumococci but inadequate to prevent superinfection by *Staph. aureus* and *H. influenzae,* which the patient was probably carrying at the same time. Whether or not the organisms isolated post mortem were in fact resistant to the antibiotics administered was not determined, but this is suggested by the bacteriologic findings.

Dr. Castleman: One gathers from the record that the severe infection was perhaps not recognized clinically and that perhaps the patient did not get adequate antibiotic treatment. He received 1 gm. of streptomycin and 300,000 units of Crysticillin on the first day and 1.5 gm. of streptomycin and 600,000 units of Crysticillin on the second day and another 1.5 gm. and 600,000 units on the third day.

Dr. N. J. Ehrenkranz: We considered the possibility of infection in the lungs because, in spite of moderate dehydration, the patient had suddenly experienced acute pulmonary edema. A pulmonary embolism seemed equally likely. About the antibiotic therapy, we believed that the patient received adequate penicillin and streptomycin, in view of the greatly impaired renal function as evidenced by a nonprotein nitrogen of 223 mg. per 100 cc. and the limited urine output of less than 400 cc. a day.

Dr. Fred Goetz: Did you find any evidence of salt depletion?

Dr. Ehrenkranz: The ward did do a sodium-balance study on the previous admission. On a 500-mg. diet the patient excreted but a few milligrams of sodium in the urine, and the serum sodium level actually rose. In severe heart failure low sodium levels are not unusual.

CASE 40252

Presentation of Case

A seventy-three-year-old housewife was admitted to the Emergency Ward because of jaundice.

Five days previously she felt somewhat apathetic, without a specific complaint. On the following day she experienced a sudden, severe epigastric pain, which radiated through to the back and subsequently waxed and waned until admission. Two days later she had a chill and vomited. It was noted that she was jaundiced, that stools were light colored and that the urine was dark.

Three years before admission a left radical mastectomy had been performed for carcinoma. The liver edge was found to be 3 fingerbreadths below the right costal margin, but there was no evidence of metastases at that time and sixteen lymph nodes were reported as negative. Hypertension (blood pressure of 180 systolic, 95 diastolic) and mild diabetes mellitus were also discovered, and she had been followed in the diabetic and tumor clinics, a palpable liver edge again being noted a year before entry.

Physical examination disclosed a well developed and well nourished woman who was jaundiced but in no severe distress. The mastectomy scar showed a few small areas of granulation tissue, but there was no evidence of tumor recurrence. A Grade 3 systolic murmur was heard over the aortic area. The liver edge was 4 fingerbreadths below the right costal margin, with a hard lump at the midclavicular line. There was tenderness over the epigastrium on the right.

The temperature was 100°F., the pulse 76, and the respirations 30. The blood pressure was 210 systolic, 85 diastolic.

The urine gave a + + + + reaction for bile, a + + + reaction for albumin and a yellow-green test for sugar. The sediment contained 2 to 5 white cells and a few granular casts per high-power field. Examination of the blood revealed a hemoglobin of 14.8 gm. per 100 cc. and a white-cell count of 9100. The serum total protein was 6.0 gm., the albumin 3.4 gm., the globulin 2.6 gm., the amylase 13 Russell units (normal 8 to 18 Russell units), the nonprotein nitrogen 20 mg., the serum total bilirubin 9.0 mg., and the alkaline phosphatase 6.8 units per 100 cc.; the sodium was 135 milliequiv., the potassium 3.4 milliequiv., the chloride 97 milliequiv., and the carbon dioxide 28 milliequiv. per liter. The cephalin flocculation was + + in twenty-four and + + + in forty-eight hours. A stool specimen was guaiac negative. A plain film of the abdomen was normal except for a 7-cm., ring-like density in the right midportion of the abdomen just lateral to the third lumbar vertebra (Fig. 1). A roentgenogram of the chest showed only a few strands of increased density.

An operation was performed.

Differential Diagnosis

Dr. Warren Point*: To begin with, this patient had a calcified, ring-like area in the right upper quadrant and apparently had an infection of some sort with sudden onset of jaundice, chills and fever. The past history of a carcinoma of the breast removed three years before admission is confusing, and although there were no signs of metastases then or on admission, one should keep the possibility in mind. I should like to ask if the patient was born in this country or in the Mediterranean.

*Assistant in medicine, Massachusetts General Hospital.

Dr. Benjamin Castleman: She was born in this country.

Dr. Point: There goes one possible diagnosis "down the drain."

I should like to see this intriguing mass in the x-ray films.

Dr. John F. Gibbons: The ring-like shadow is obvious in the right upper quadrant (Fig. 1). There are also some punctate calcific densities within the ring of calcium. The liver edge can be seen, and the liver probably is not enlarged, nor does the spleen appear to be enlarged. The psoas-muscle shadows can be seen through the gas and fecal débris in the colon, and the renal outlines appear normal in shape and size.

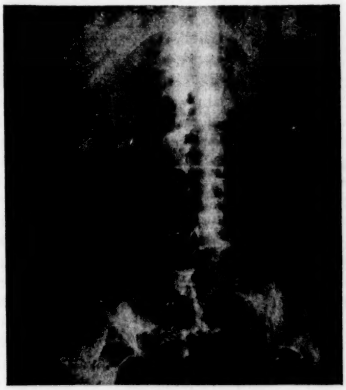


Figure 1. *Plain Roentgenogram of the Abdomen, Showing Ovoid Mass in the Right Upper Quadrant with Calcification in Its Wall.*

Dr. Point: Do you see any signs of a biliary-duct stone?

Dr. Gibbons: No; I do not.

Dr. Point: Do you think the calcified mass is part of the liver or distinct from the liver?

Dr. Gibbons: There is no obvious connection to the liver. I can only say that it overlies the lower edge of the liver as I see it in one projection.

Dr. Point: Although there is no lateral film can you tell whether the mass is retroperitoneal or intraperitoneal?

Dr. Gibbons: I can only say that the psoas-muscle shadow and renal shadow appear to be normal in outline and not displaced or compressed by the mass, which means to me that it is probably intraperitoneal rather than retroperitoneal.

Dr. Point: The first problem to settle is whether the patient had jaundice of a hepatocellular or obstructive type. The only evidence for jaundice of hepatocellular origin—cirrhosis or hepatitis—is the slightly elevated serum globulin of 2.6 gm. per 100 cc.

and the cephalin flocculation of + + + in forty-eight hours; the physical examination, the past history and the laboratory tests do not point to cirrhosis. There was no large spleen and no other corollary evidence of cirrhosis such as palmar erythema, spider angiomas, slick tongue or collateral circulation, so I shall discount cirrhosis as the cause of jaundice. Could this have been hepatitis? The course and the patient's age are unusual for hepatitis. Knowing no more about the recent past than I do, I doubt if she had hepatic disease of the homologous-serum or the usual epidemic type. I shall therefore eliminate cirrhosis and hepatitis.

I suspect that this patient had obstructive jaundice, with, in all probability, cholangitis to account for the sudden onset of the right-upper-quadrant pain radiating through to the back. I do not know to what part of the back the pain went but at least it radiated to the back. The pain was associated shortly thereafter with the onset of chills and fever, which usually indicate bacterial infection. There may be similar symptoms at times in the very beginning of infectious hepatitis, but I believe the jaundice was obstructive.

Could she have had pancreatitis? I do not see any evidence for that although she did have back pain with the onset of the difficulty, which may have been midline. The amylase was perfectly normal for that method. I might mention that the Russell method was chosen because the patient was diabetic and had an elevated blood sugar so that the usual procedure was not practical. There was no evidence that she had pancreatitis or pancreatic carcinoma to account for obstructive jaundice. I do not see a gastrointestinal x-ray series to help me outline the head of the pancreas, or a barium-swallow examination to rule esophageal varices and the diagnosis of cirrhosis in or out. Possibly, this mass was pancreatitic in origin but it would be very unusual and more than coincidental for it to be on the right side. So I shall rule out the pancreas as the cause of the jaundice.

Could it have been carcinoma of the ampulla of Vater? The picture that she presented on entry, to my mind, was principally that of biliary-tract obstruction with resultant cholangitis, and not of carcinoma of the ampulla. Obviously, then, I have to postulate that she had a gallstone that had "popped" on down and caused an obstruction. It would be interesting to know whether the stools were brown, white or black? I suspect and hope that they were probably very light in color.

DR. CASTLEMAN: The stools were light brown and guaiac negative.

DR. POINT: Apparently, some bile was going into the gastrointestinal tract; therefore, I have to postulate a ball-valve action at the ampulla of Vater.

Now I come to what I am sure is the meat of this problem—that is, the nature of the calcified ring in the upper quadrant. This, of course, may be a "red herring." If I try to tie together the calcified ring with the present symptoms, I naturally think about some condition in the biliary tree. Could it have been a choledochal cyst? That is an unusual congenital anomaly and is usually seen in patients below the age of fifteen. I do not know whether they become calcified. I do not believe that this patient had that.

Could she have had a peritoneal, mesenteric or omental cyst? That could account for the shadow, but again I do not know if they become calcified. The reference[1] that I consulted did not mention calcification in the cysts, and it would not fit very well with the other findings, so that I tend to disregard peritoneal, omental and mesenteric cysts as the cause of the difficulty.

The next question that arises is whether the calcification was inside or outside the liver. The information that I have been given indicates that it was probably outside the liver although it could have been a pedunculated cystic mass of the liver itself. If that were so one would think of a hydatid cyst, but the fact that the patient was not born in the Mediterranean area is of course good evidence against a hydatid cyst. This was a cystic mass that was calcified in spotty fashion; I gather that the calcified mass was the lump that was felt beneath the right margin of the liver in the midclavicular line. Hydatid cysts that are near the anterior surface of the liver are commonly palpated in that region. If this had been a hydatid cyst it would be extremely difficult to connect the acute illness with the hydatid cyst unless there was secondary infection in the cyst or unless the cyst was of the very rare alveolar type, in which there is massive fleshy extension outward to involve the bile radicles. That is so rare that I think I had better forget about it.

What other processes in the liver might calcify like this? Benign tumors such as adenomas, angiomas and lipomas may calcify, but again I cannot connect them with the present illness nor do I believe that they would calcify to this extent; therefore I am tempted to disregard them.

Could this have been metastatic carcinoma from the breast to the liver, with mechanical embarrassment of the biliary tree? The liver is not uncommonly involved in metastatic carcinoma, but there was no evidence of carcinoma elsewhere. Then, too, tumors of metastatic origin in the liver are usually not calcified. Although I think I am being led to the diagnosis of carcinoma of the breast metastatic to the liver, I shall disregard that diagnosis.

Could this have been a syphilitic gumma or an abscess? Again, that is unlikely, and it does not explain the picture so I shall disregard that too.

To go back to the biliary tree, there are other conditions that could produce this picture. Could it have been a solitary gallstone composed of cholesterol in the middle and calcified on the outside? Indeed, it is said in one textbook of radiology[2] that stones sometimes look like that with a ring around them, but they

vary from the size of a pea up to 2 cm. in diameter. It seems unlikely that the mass was a gallstone. If this was a gallstone, did she have another that obstructed the bile duct?

Finally, a very unusual situation is the so-called porcelain gall bladder. In this condition there is calcification of the gall-bladder mucosa, usually with stones in the bladder. The gall bladder tends to become a cystic organ in that the cystic duct is often obliterated, and this seems to allow the gall bladder to become distended and palpable. It is not uncommon to feel the gall bladder beneath the liver in such a condition. I have never seen this condition, but certainly this picture might fit what I have read about it. This would also help me explain why the patient had obstructive jaundice because I shall postulate that she had cholecystitis with porcelain gall bladder and that a gallstone dropped down into the biliary tree and caused obstructive jaundice and cholangitis. That will be my diagnosis. It may well be that this mass was a "red herring" and had no relation to the acute illness, but I shall tie them together in that way.

DR. CASTLEMAN: It is obvious that Dr. Point did a great deal of reading of the literature in preparing this case.

Would you have operated on the patient immediately, Dr. Point? Or did you have some reservation that this might have been a form of hepatocellular disease and therefore, would you have resorted to an aspiration liver biopsy before operation?

DR. POINT: I should have liked to see the patient before I made such a decision. I suspect the operation was an exploration rather than an aspiration liver biopsy.

CLINICAL DIAGNOSIS

Calcified gall bladder.

DR. WARREN POINT'S DIAGNOSES

Chronic cholecystitis, with calcified gall bladder.
Cholelithiasis and choledocholithiasis.

ANATOMICAL DIAGNOSES

Chronic cholecystitis, with calcified gall bladder.
Cholelithiasis and choledocholithiasis.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: A liver biopsy was not done; the patient was explored. The mass that was removed was extremely hard, calcified and rigid and proved to be, as Dr. Point suggested, a porcelain-like gall bladder, with extensive calcification throughout its entire wall as well as in the mucosa. There were also,

FIGURE 2.

as Dr. Point predicted, many stones in the gall bladder. None were impacted in the cystic duct at the time of operation, but one was impacted in the ampulla of Vater so that the surgeon had to explore the common duct and crush the stone in the ampulla to allow for flow of bile into the common bile duct. This is a relatively rare type of gall-bladder disease; I can recall only 3 cases. Usually, it is due to a stone impacted in the cystic duct that produces hydrops first, with secondary deposition of calcium as a result of chronic infection. Occasionally, it is seen with so-called milk bile where the calcium carbonate of the bile lines the mucosa of the gall bladder. This film taken of the gall bladder after removal demonstrates the extensive involvement of the wall itself (Fig. 2). It is interesting that when the patient was first seen before an x-ray film was taken, because of the history of cancer of the breast and the presence of jaundice most examiners believed that this mass was a huge metastatic nodule in the liver.

Postoperatively the jaundice was much less on the fourth day, and a cholangiogram on the seventh day showed free flow of bile into the duodenum and reflux into the biliary tree.

REFERENCES

1. Bockus, H. L. *Gastro-enterology.* Vol. 2. 975 pp. Philadelphia: Saunders, 1944.
2. *A Text-Book of X-Ray Diagnosis.* Second edition. Vol. 3. 830 pp. Edited by S. C. Shanks and P. J. Kerley. Philadelphia: Saunders, 1950.

The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. — Richard E. Alt, M.D.
Oliver Cope, M.D. — James M. Faulkner, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. — Donald Munro, M.D.
Theodore H. Ingalls, M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR
James F. Ballard, BOOK REVIEW EDITOR
Milton C. Paige, Jr., BUSINESS MANAGER

EDITORIAL BOARD
Henry R. Viets, M.D. — Benjamin Castleman, M.D.
Robert M. Green, M.D. — Hugh R. Leavell, M.D.
Dwight O'Hara, M.D. — J. Englebert Dunphy, M.D.
Fletcher H. Colby, M.D. — Robert W. Buck, M.D.
Robert L. Goodale, M.D. — Herman L. Blumgart, M.D.
Chester M. Jones, M.D. — Frank N. Allan, M.D.
Harvey R. Morrison, M.D. — Harvey A. Kelly, M.D.
Maxwell Finland, M.D. — Langdon Parsons, M.D.
Vernon P. Williams, M.D. — Deering G. Smith, M.D.*
*Representing the New Hampshire Medical Society.

SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (first-year interns and medical students, $5.00 per year); Canada, $9.00 per year (Boston funds); foreign, $10.50 per year. Long-term rates: United States, 2 years $15.00, 3 years $22.00; Canada, 2 years $17.00, 3 years $25.00; foreign, 2 years $20.00, 3 years $29.50.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

FELLOWSHIP IN THE BOSTON MEDICAL LIBRARY

IT is no secret that the Boston Medical Library is putting its house in order and in the process has received an astonishing amount of support. The success of its recent fund-raising campaign was announced late last year, and before the close of the present year that success will be converted into the necessary material improvements.

The next step will be in the direction of improved service and will consist mainly of adding to the present trained but overworked personnel equally trained reinforcements. The long view envisions a sufficient endowment, which must be gradually accumulated by gift and legacy, but of more immediate concern is an increase in the regular annual income that is derived from the active and responsible members of the medical community.

The Massachusetts Medical Society has already met this responsibility in its official capacity by guaranteeing to the Library an annual $5 membership for each of its active fellows; over and above this income must be that from the dues of a solid core of voluntary fellows of the Library, gladly accepting the additional responsibility of comprising the corporation of this venerable, dignified and irreplaceable institution.

To this end a considerable number of physicians who have shown an interest in the Library have been invited by the trustees to become fellows. It is hoped that others who may not yet have shown this interest will be inspired to apply for such fellowship, recognizing that, in most cases, it will represent an annual contribution in addition to that which is more or less automatically made as a Massachusetts Medical Society member.

The Boston Medical Library has been serving this area efficiently and quietly for over three quarters of a century. With the admirable restraint of a decorous New England institution it has maintained high quality of service and its position in the medical field with little benefit of press and none of radio. Unobtrusiveness has not meant obscurity, however, for inquiries and visitors from all over the world are a part of the daily pattern, and the calls for information, for books and for periodicals are unceasing.

The Library is a living monument to the past and a guarantee of the future of New England medicine in which every New England physician may take pride. To copy an apt quotation from another, more obscure monument, "What is excellent, as God lives, is permanent."

SCRAPING THE BARREL

FORTY years ago the chief qualifications for admission to the best medical schools in the country were little more than the satisfactory completion of a minimum number of premedical courses and the desire to study medicine. This type and degree of academic freedom gradually became less and less operative to the point where, during and just after the war, the better schools were able to accept only about one in seven of their applicants. This period was already drawing to its close when the clamor for more doctors and more schools to produce them reached its highest pitch.

The situation has already been discussed, notably in the editorial column of the August 13, 1953, issue of the *Journal*, where it was pointed out that already the applicants for admission to medical schools had declined for the academic year 1952-1953 more than 30 per cent below the number applying for 1949-1950. The decline, it was noted, occurred in a period when many of the schools had increased their teaching facilities.

Information on this trend is brought up to date by John M. Stalnaker, writing in the *Journal of Medical Education* for April of this year. Whereas approved schools of medicine are now accepting their largest first-year classes—amounting to nearly 7500 students

—the number of applicants for admission has declined for the fourth consecutive year. Thus, the class that entered in the fall of 1953 had over 2000 fewer applicants than the class that entered in 1952, and nearly 10,000 fewer than applied in 1949.

More students are still applying than can be accepted, which is the only argument necessary for the politicians who still labor in the interest of more, if not of better, schools; the important point is that the over-all quality of the student body is not up to its best standards, when many were called but few were chosen. Running into particular difficulties are those schools that limit their applications to residents of the state in which the institution is established. In these cases, according to the well worn but still graphic cliché, the bottom of the barrel is really being scraped.

FOOD FOR THE FUTURE

THE House of Lords, according to an annotation in the *British Medical Journal* a few weeks ago, is seriously concerned over the world's future food supply and has taken steps to solve the problem. Impressed by the report that the blue whale, on a diet of plankton alone, can achieve a length of 60 feet and a weight of 50 tons in two years, starting at something better than scratch, the idea has developed that the whale may be forestalled in his search for diatoms and that these tasty morsels can be diverted to human use.

Plankton, scarcely known to the average human being until publicized by the *Kontiki* seafarers and Rachel Carson, was described by Herman Melville over a hundred years ago, although not under that name, as resembling waves of amber grain spreading over vast areas of the South Pacific. Long known as a source of food for the denizens of the deep, plankton was hardly thought of for human consumption until the crew of *Kontiki* substituted it for alphabet and other kinds of soup. Any resemblance between plankton and planktsteak, however, is said to be purely accidental.

A practical difficulty in the way of substituting plankton for sirloin is the fact that 30 tons of sea water need to be finely filtered to produce an ounce of the dried algae. Artificial cultivation, however, is already under way, both in Britain and in America, where the alga *Chlorella* is being currently cultivated on a laboratory roof in Cambridge, Massachusetts. Grown in a curved polyethylene tube, 160 feet long, *Chlorella* is suspended in a culture medium containing nitrogen and air mixed with a high content of carbon dioxide. An acre can be made to produce an annual crop of 40 tons of dried pabulum containing 50 per cent of protein and 7 per cent of fat, costing probably 25 to 30 cents per pound. It is alleged that if the yield can be doubled and the cost halved this form of nourishment may become highly competitive in a free market.

No statement is included regarding methods of preparation for the table, or of serving. In the opinion of some gourmets *Chlorella* will have little difficulty in competing with buttered parsnips.

NO REST FOR THE WEARY

FEW may recall, without recourse to *Bartlett's Familiar Quotations*, those dismal lines of William Rose Benét's that run:

> One speck within vast star-space lying
> Awoke, arose, resumed its clothing,
> And crawled another day toward dying.

One's attitude toward this prospect, so depressingly stated, must depend on one's point of view of the moment, however; at least the crawl has become a longer one to a more distant goal.

Certain facts that bear on man's endurance run and his capacity for enduring it have been brought out by the somewhat startled statisticians of the Metropolitan Life Insurance Company. According to the figures produced by this corps of experts at least 60 per cent of all men between the ages of sixty-five and sixty-nine, and fully 40 per cent of those from seventy to seventy-four, are still gainfully employed, refuting the common belief that most men work no more after three score years and five. Indeed, 20 per cent of those at seventy-five and over still have their daily encounter with the time clock.

About four fifths of these workers are employed full time; more of them are self-employed than at younger ages, and more are employed as farmers and farm managers, executives and such service workers as watchmen and guards.

As the statisticians sagely conclude, "the chances of survival to the older ages have increased markedly, and to make adequate provision for this period calls for a program of careful planning and savings during the productive years."

Dr. Hobbs, of Memphis, insists upon a discovery he has made, that the use of cistern water *in that city, exclusively, will prevent the cholera.*
Boston M. & S. J., *June 28, 1854*

MASSACHUSETTS MEDICAL SOCIETY

VACCINIA-IMMUNE GAMMA GLOBULIN

The American National Red Cross has just announced the availability of a new blood serum concentrate called vaccinia-immune gamma globulin. This was developed by Dr. C. Henry Kempe, of the

University of California School of Medicine, and is useful for the prevention and treatment of rare but serious complications of smallpox vaccination.

This material, which will be distributed free by the Red Cross, may be obtained by any physician who will write over his signature, identifying himself as a licensed physician, to Dr. Sam T. Gibson, associate director, Blood Program, American Red Cross, National Headquarters, Washington, D. C., stating the amount of the material desired and the address to which it should be sent.

The Massachusetts Medical Society Committee on Supervision of the Red Cross Blood Program adds the statement that regular immune globulin is also valuable in these complications of smallpox vaccination and may be used to begin treatment before arrival of the vaccinia-immune gamma globulin.

DEATHS

GAUNT — George A. Gaunt, M.D., of Boston, died on May 27. He was in his sixty-fourth year.

Dr. Gaunt received his degree from the College of Physicians and Surgeons, Boston, in 1916. He was a member of the staff of the Neuropsychiatric Unit of the Veterans Administration, the American Psychiatric Association and the New England Society of Psychiatry and a fellow of the American Medical Association.

HOMANS — John Homans, M.D., of Brookline, died on June 7. He was in his seventy-seventh year.

Dr. Homans received his degree from Harvard Medical School in 1903. He was a member of the American Surgical Association, New England Surgical Society and the staff of the Peter Bent Brigham Hospital, a fellow of the American Medical Association and clinical professor of surgery, emeritus, at Harvard Medical School.

He is survived by his widow, a daughter, a son, two sisters and a brother.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

POLICY ON DISTRIBUTION OF POLIOMYELITIS-IMMUNE GLOBULIN IN 1954

The following statement represents the policy of the Department on distribution of gamma globulin.

The value of gamma globulin in the prevention of the paralysis of poliomyelitis under present-day working conditions is probably negligible. This is due to the inability to determine the status of any particular person. Many persons have already acquired immunity, and the gamma globulin is wasted. In others, who are already in the incubation stage, the product will not affect the course of the disease. Some have not been and will not be effectively exposed during the three to five weeks in which the globulin will be effective.

Nevertheless, the product has been made available for administration in poliomyelitis in 1954. To make the best use of its slight value some comments and suggestions are made.

The dosage this year has been increased from 0.14 to 0.2 cc. per pound of body weight. This will mean that a person weighing 150 pounds receives 30 cc. This is the maximum dose also for a person of heavier weight. The 30 cc. represents the gamma globulin from four Red Cross blood donations.

Because nearly three quarters of the multiple cases of poliomyelitis in households are co-primary, instead of 1 case that is secondary, little value can be expected from the use of gamma globulin in household contacts. For this reason administration to family contacts is discouraged. More value may result from administration of the product to those who are on the fringe of the family circle, such as those living in the same duplex or small apartment house, next-door neighbors who mingle regularly with the family circle, visitors who have spent some hours in the household, caten meals or had other intimate contact with members of the household. This is on the supposition that such persons may not yet have been exposed. The supply of poliomyelitis-immune globulin is not unlimited, of course, and in order that the circle around each case may not become too large and the drain on the supply too great the following priority list should be kept in mind:

1. Pregnant women who have been in contact with a household in which a case has occurred.
2. Pregnant women in communities where the disease is prevalent.
3. Persons who are caring for a patient in the first week of illness.
4. New arrivals in an infected household (those who have not been there for more than four days).
5. Visitors who have spent some time in an infected household or have eaten a meal there within the last four days.
6. Households in the same duplex, apartment house or next-door single house, when there has been visiting back and forth.
7. Persons who have spent only a short time in an infected household.

Some attempt has been made to place these in a descending order of importance. Other illustrations could be cited that would be placed somewhere in this list, which is intended to be merely suggestive and not exhaustive.

Brief contacts in open air, on street cars and buses, in stores, theaters, public buildings, large gatherings and so forth are probably seldom important.

The giving of gamma globulin every three to five weeks during the season without valid exposure is not recognized as a reasonable use of the product.

Since it will be impossible for the Department or local board of health to investigate every person for whom the product may be requested, physicians are asked to limit its use to a reasonable number of persons in contact with each case.

The only record kept this year will contain the name of the physician, the name of the patient, the number of persons to be given gamma globulin and the total amount requested. These records will remain on file both locally and in the Department, and will be open to anyone who wishes to see how the supply has been used. Supplies will not be issued to physicians to be kept on hand in case of need.

IMMUNE SERUM GLOBULIN

The Department receives many inquiries regarding immune serum globulin. Since this material becomes poliomyelitis-immune globulin after having passed a test against the Lansing (Type 2) strain of poliomyelitis virus, this has been the cause of some confusion among the medical profession. The following summary of the present status of immune serum globulin is an attempt to answer some of the more commonly asked questions.

Source

The human blood from which the globulin fraction is separated is obtained from the donor in either of two ways: the blood may be collected by venipuncture; or the blood may be collected incidental to the expulsion of the human placenta at the time of childbirth and from the placenta itself.

In either event the donors must meet requirements for health, and the final product must pass the same minimum requirements of the National Institutes of Health, regardless of source. Routine lots of globulin prepared from placen-

tal blood are darker in color (owing to hemoglobin) than those prepared from bloods taken by venipuncture. This color does not affect the product in any way.

Sensitivity

Unlike biologic preparations from animal sources, no sensitivity test is necessary before the administration of immune serum globulin. This material, being of human origin, requires no such testing. It must not be injected intravenously.

POLIOMYELITIS-IMMUNE GLOBULIN

This material is immune serum globulin that has passed a test required by the National Institutes of Health against the Lansing (Type 2) strain of poliomyelitis virus. Its value against measles and infectious hepatitis is equal to that of immune serum globulin. Also, it should be mentioned that any lots that fail the test against the Lansing strain are distributed as immune serum globulin. Thus, for diseases other than poliomyelitis, the two products may be used interchangeably.

DISEASE PREVENTION AND MODIFICATION

Measles

For children three years of age or under and ill or weakened children of any age, a dose of immune serum globulin of sufficient size to prevent the disease, provided the exposure is known, should be administered. Older children should be given globulin in lower dosage to modify the disease; in such cases it is hoped to produce immunity by the combined active-passive method. It is also desirable to prevent the disease in susceptible pregnant women.

The following dosage is recommended for measles: prevention, 0.1 cc. per pound of body weight up to a maximum of 15 cc., if given within six days after initial exposure; modification, 0.02 cc. per pound of body weight, if given from two to six days after initial exposure.

Infectious Hepatitis

Prevention may be justified in exposed adults who have pre-existing hepatic disease and in exposed pregnant women. For this purpose the dose is 15 cc.

In all other exposed persons the aim should be modification. For this purpose the dose of 0.01 cc. per pound of body weight, up to a maximum dose of 1 cc., has been shown to give adequate protection.

Homologous Serum Jaundice

The ability of globulin to prevent or modify this disease has not been established. In unusual cases in which exposure is known 10 cc. per month for four months may be tried.

German Measles

Although immune serum globulin has not been proved to be dependable in preventing the disease in susceptible pregnant women, its use in a dosage of 20 cc. is considered to be justified. Experimentally, immune serum globulin made from the blood of convalescents has shown much promise, but the supply itself is extremely scarce.

Agammaglobulinemia

Studies now in progress show that in this condition immune serum globulin at monthly intervals is life saving if used in large doses.

Mumps

Immune serum globulin has no value in the prevention of mumps.

Mumps convalescent serum produced commercially is available.

Chicken Pox

Immune serum globulin is of no value in this disease.

Poliomyelitis

Although the use of globulin to prevent or modify poliomyelitis has been established experimentally to the satisfaction of many scientists, its value in clinical application has not been proved. It must be continually borne in mind that any widespread use of this material for poliomyelitis will eventually prevent its being available for diseases in which it has well established value. Even if its value had been established last year in nationwide usage, its practical value as a measure for the control of poliomyelitis would remain extremely limited. Its use during the epidemic season should be restricted to pregnant women in communities in which the disease is prevalent and to contacts of cases, regardless of age.

The dosage recommended for the modification or prevention of poliomyelitis is 0.2 cc. per pound of body weight up to a maximum of 30 cc.

CORRESPONDENCE

TEN YEARS OF STREPTOMYCIN

To the Editor: Since 1914 Dr. Selman A. Waksman, of the Department of Soil Microbiology of the New Jersey Agricultural Experiment Station of Rutgers University, has made extensive investigations of the microbiologic population of the soil, devoting particular attention to a little known group of soil organisms known as actinomycetes. In 1939, he undertook a detailed study of the production by soil organisms of antibiotics, or substances destructive to other micro-organisms, a name that he coined in 1941. In 1940 he and his assistants succeeded in isolating actinomycin, the first true antibiotic produced by one of the actinomycetes. This substance was too toxic for human use. Two years later he isolated streptothricin, a much more desirable type of substance that had all the properties of an acceptable chemotherapeutic agent. It was active against both gram-positive and gram-negative bacteria not only in the test tube but also in laboratory animals. Unfortunately, this substance still had a residual toxic effect on the animal body. In pursuing the search for streptothricin-like substances Dr. Waksman, with his assistants, in September, 1943, isolated streptomycin from a strain of *Streptomyces griseus*, obtained from a swab of a chicken's throat. The first public announcement of this antibiotic agent was made in January, 1944, and in 1945 streptomycin was already recognized as a highly effective agent against various diseases caused by gram-positive and gram-negative bacteria, including the tuberculosis organism, not only *in vitro* but also *in vivo*.

Within ten years the production of streptomycin has grown from a laboratory curiosity to a multi-million-dollar industry. Nine companies are engaged in its manufacture in this country alone, with at least 20 other plants in foreign countries. The royalties accruing to the Rutgers Research and Endowment Foundation from the production of streptomycin in the United States have been used largely for the building of an Institute of Microbiology at Rutgers University. The $3,500,000 structure of the Institute was dedicated on June 7 of this year.

SOLOMON R. KAGAN, M.D., Sc.D.
Roxbury, Massachusetts

BOOK REVIEWS

Psychosomatic Research. By Roy R. Grinker, M.D. 8°, cloth, 207 pp. New York: W. W. Norton and Company, Incorporated, 1953. $3.50.

One of the dominant theories in medical science during the last twenty-five years is the changing concept of body-mind relations. Early work at Harvard by the late Professor Walter B. Cannon stimulated further studies by Dr. Flanders Dunbar and later workers. Now comes the most complete and up-to-date appraisal of current concepts by a physician who is a research worker and pioneer in this field. Since his brilliant efforts in military service during World War II Dr. Grinker has devoted himself mainly to a review of

further developments in psychosomatic research.

This book is basic reading for every physician who is interested in keeping abreast of new developments in this area.

The second chapter, entitled "Historical Concepts," is as fascinating as a discourse by Aesculapius himself. Especially useful to the clinician are the eleventh chapter, which emphasizes anxiety, and the twelfth, which gives the author's conclusions. This book cannot be superficially described or condensed but must be read to be appreciated.

MERRILL MOORE, M.D.

Heredity in Health and Mental Disorders: Principles of psychiatric genetics in the light of comparative twin studies. By Franz J. Kallmann, M.D. With a foreword by Nolan D. C. Lewis, M.D. 8°, cloth, 315 pp., with 89 illustrations and 20 tables. New York: W. W. Norton and Company, Incorporated, 1953. $6.00.

Certain questions always arise when physicians take the family history in any case of mental disorder: What is "hereditary" in this situation, and what may not be considered hereditary? Dr. Kallmann tries to answer these questions from a new approach. He has adopted principles of psychiatric genetics in the light of comparative twin studies on a scale larger than any used before. His section on the modern history and general principles of genetics is classic and well worth reading.

As a whole the book is technical, but there are points that, in turn, will be of special interest to the psychiatrist, the psychologist and the social worker, as well as to the general practitioner who remembers his basic biology and is still interested in it. The illustrations are especially remarkable—some of the conditions illustrated have not previously been presented. This work is the outcome of Dr. Kallmann's earliest studies on the problems of schizophrenia, and in this book he brings together for the first time some of the results of this work.

MERRILL MOORE, M.D.

NOTICES

INTERNATIONAL ACADEMY OF PROCTOLOGY 1954-1955 AWARD CONTEST

The International Academy of Proctology will award $100 and a certificate of merit for the best unpublished contribution on proctology or allied subjects. The competition is open to all physicians in all countries. All entries, which should be limited to 5000 words, typewritten in English, submitted in five copies and received before February 1, 1955, should be addressed to the International Academy of Proctology, 43-55 Kissena Boulevard, Flushing, New York. The prizes and certificates will be presented at the annual convention dinner dance in March, 1955.

INTERNATIONAL SYMPOSIUM ON THE HYPOPHYSEAL GROWTH HORMONE

An international symposium on the hypophyseal growth hormone, its nature and actions will be sponsored by the Henry Ford Hospital and the Edsel B. Ford Institute for Medical Research in the New Clinic Building Auditorium, Henry Ford Hospital, Detroit, October 27 through 29. The following aspects of growth-hormone investigation will be considered: bioassay, preparation and physicochemical properties of growth hormone; effects of growth hormone on certain structures such as the mammary gland, skeletal system, connective tissue, islands of Langerhans, kidneys, gastrointestinal tract and tissue cultures; growth-hormone and energy sources; the effect of growth hormone on cellular systems; the influence of growth hormone on lactation; and the metabolic effects in man.

Invitations may be obtained from the Program Committee, Henry Ford Hospital, Detroit 2, Michigan.

MASSACHUSETTS GENERAL HOSPITAL HAND CLINIC

The Massachusetts General Hospital announces that the consultation services of the Hand Clinic are now available for referrals of patients in all income categories. Patients will be seen by appointment, every Wednesday at 1 p.m.

AMERICAN OCCUPATIONAL THERAPY ASSOCIATION

The thirty-seventh annual conference of the American Occupational Therapy Association will be held at the Shoreham Hotel, Washington, D.C., October 16-22. The theme of the general conference will be "Capitalize Your Assets."

PAN-PACIFIC SURGICAL ASSOCIATION

The sixth congress of the Pan-Pacific Surgical Association will be held in Honolulu, October 7 and 8. All hotel and travel reservations should be made through Dr. F. J. Pinkerton, Director General, Pan-Pacific Surgical Association, Suite 7, Young Building, Honolulu, Hawaii.

AMERICAN ACADEMY OF DENTAL MEDICINE

The ninth semiannual meeting of the American Academy of Dental Medicine will be held at the Hotel Statler, New York City, on December 5 at 12:30 p.m. The business meeting for members will be held at 10:30 a.m. A symposium on bone will be held from 2 to 5 p.m. All interested physicians and dentists are invited. Reservations may be made with the national secretary, Dr. William M. Greenhut, 124 East 84th Street, New York 28, New York.

UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE

The annual assembly in otolaryngology, sponsored by the Department of Otolaryngology, University of Illinois College of Medicine, will be held in Chicago, September 6 to 11. The meeting will be devoted to surgical anatomy and cadaver dissection of the head and neck and histopathology of the ear, nose and throat, and will be under the direction of Dr. Maurice F. Snitman. Registration will be limited and information may be obtained from the Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

SOCIETY MEETINGS AND CONFERENCES

JULY 6–AUGUST 23. Consultation Clinics for Crippled Children in Massachusetts. Page 1054, issue of June 17.

JULY 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

JULY 23–29. International Cancer Congress. Page 914, issue of November 26.

JULY 26–31. International Congress of Gynecology and Obstetrics. Page 400, issue of March 4.

AUGUST 1–7. Pan-American Congress of Pediatrics. Page 850, issue of May 13.

AUGUST 17–20. Argentine Congress of Thoracic Surgery. Page 708, issue of April 22.

SEPTEMBER 6–10. International Poliomyelitis Congress. Page 399, issue of March 4.

SEPTEMBER 6–11. University of Illinois College of Medicine. Annual Assembly in Otolaryngology. Notice above.

SEPTEMBER 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

SEPTEMBER 12–15. Second International Congress of Cardiology. Washington, D. C.

SEPTEMBER 13–15. American Association of Blood Banks. Page 968, issue of June 3.

SEPTEMBER 16–18. American Heart Association. Annual Scientific Sessions. Washington, D. C.

SEPTEMBER 22. New England Pediatric Society. Page 968, issue of June 3.

OCTOBER 1 and DECEMBER 3, 1954; FEBRUARY 4 and APRIL 1, 1955. New England Society of Anesthesiologists. Page 1054, issue of June 17.

OCTOBER 7 and 8. Pan-Pacific Surgical Association. Notice above.

(Notices concluded on page xxiii)